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(54) Title: HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

(57) Abstract: The present invention features substantially pure HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), an HDRP(ΔNLS) polypeptides, and isolated nucleic acid molecules encoding those polypeptides. The present invention also features vectors containing*HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid sequences, and cells containing those vectors.

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HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/298,173 filed on June 14, 2001, U.S. Provisional Application No. 60/311,686 filed on August 10, 2001, and U.S. Provisional Application No. 60/316,995, filed on September 4, 2001. The entire teachings of the above applications are incorporated herein by reference.

GOVERNMENT SUPPORT

The invention was supported, in whole or in part, by grant CA-0974823 from the National Cancer Institute. The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

The N-terminal tails of core histones are covalently modified by post-translational modifications, including acetylation and phosphorylation. Evidence suggests that these covalent modifications play important roles in several biological activities involving chromatin, *e.g.*, transcription and replication. Histone deacetylases (HDACs) catalyze the removal of the acetyl group from the lysine residues in the N-terminal tails of nucleosomal core histones resulting in a more compact chromatin structure, a configuration that is generally associated with repression of transcription.

Five proteins and/or open reading frames in yeast (RPD3, HDA1, HOS1, HOS2 and HOS3) that share significant homology in the catalytic domain have been identified as HDACs based upon their sequence homology to human HDAC1. To date, eight HDACs have been identified in mammalian cells, and classified into two classes based on their structure and similarity to yeast RPD3 or HDA1 proteins. Recently, Sir2 family proteins that are structurally unrelated to the five proteins aforementioned have been identified as NAD-dependent HDACs. Class I HDACs are the yeast RPD3 homologs HDAC1, 2, 3, and 8, and are composed primarily of a catalytic domain. Class II HDACs are the yeast HDA1 homologs HDAC4, 5, 6, and

7. HDAC4, 5, and 7 contain a long non-catalytic N-terminal end and a C-terminal HDAC catalytic domain while HDAC6 has two HDAC catalytic domains.

It has also been determined that histone deacetylases can be sensitive to small molecules, including trichostatin A (TSA), trapoxin, and butyrate. For example, the yeast RPD3 and HDA1 and mammalian HDAC1, 2, 3, 4, 5, 6, 7 and 8 are sensitive to inhibition by trichostatin A (TSA). The Sir2 family HDACs, yeast HOS3 and *Drosophila melanogaster* dHDAC6, however, appear to be relatively insensitive to TSA. A class of hybrid bipolar compounds, such as suberoylanilide hydroxamic acid (SAHA) have also been shown to inhibit histone deacetylases and induce terminal differentiation and/or apoptosis in various transformed cells. Examples of such compounds can be found in U.S. Patent Nos. 5,369,108, issued on November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, as well as U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, the entire content of all of which are hereby incorporated by reference.

The identification of the mechanisms by which histones are deacetylated, and the characterization of histone deacetylase function would be of great benefit in understanding how gene transcription is controlled, how the cell cycle is regulated, and how cells are signaled to undergo terminal differentiation and/or apoptosis. Elucidation of such mechanisms can lead to improved therapeutics for many diseases, in particular those characterized by cell proliferation or a lack of cell differentiation or apoptosis, for example, cancer.

SUMMARY OF THE INVENTION

The present invention relates to isolated or recombinant histone deacetylase polypeptides, and isolated histone deacetylase nucleic acid molecules encoding those polypeptides, as well as vectors and cells containing those isolated nucleic acid molecules.

In one aspect of the invention, the isolated or recombinant histone deacetylase polypeptide is selected from a) an isolated or recombinant polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and b) a polypeptide having at least 60% sequence identity with any one

of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. In one embodiment, the isolated or recombinant histone deacetylase polypeptide consists of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. In another embodiment, the isolated or recombinant histone deacetylase polypeptide is mammalian; preferably, the isolated or recombinant histone deacetylase polypeptide is human.

In another aspect, the invention features an isolated nucleic acid molecule selected from a) an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; b) a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; c) an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; d) a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; e) a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; or f) a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, or SEQ ID NO: 7; and g) an isolated nucleic acid molecule that has at least 55% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof. In one embodiment, the isolated nucleic acid molecule consists of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9. In another embodiment, the isolated nucleic acid molecule is mammalian; preferably, the isolated nucleic acid molecule is human.

In other aspects, the invention features a vector comprising the isolated histone deacetylase nucleic acid molecule described above, a cell comprising the vector, and a cell comprising the isolated histone deacetylase nucleic acid molecule described above.

In another aspect, the invention features a purified antibody that selectively binds a histone deacetylase polypeptide described above.

In yet another aspect, the invention features a method of identifying a compound that modulates expression of a histone deacetylase nucleic acid molecule described above. The method comprises the steps of a) contacting the nucleic acid molecule with a candidate compound under conditions suitable for expression; and b) assessing the level of expression of the nucleic acid molecule. A candidate compound that increases or decreases expression of the nucleic acid molecule relative to a control is a compound that modulates expression of the nucleic acid molecule. In one embodiment, the method is carried out in a cell or animal. In another embodiment, the method is carried out in a cell free system.

The invention also features a method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, for example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer and myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, and chronic myelogenous leukemia in an individual, comprising administering a compound identified by the above method.

In still another aspect, the invention features a method of identifying a compound that modulates the enzymatic activity of the histone deacetylase polypeptide described above. The method comprises the steps of a) contacting the polypeptide with a candidate compound under conditions suitable for enzymatic reaction; and b) assessing the activity level of the polypeptide. A candidate compound that increases or decreases the activity level of the polypeptide relative to a control is a compound that modulates the enzymatic activity of the polypeptide. In one embodiment, the method is carried out in a cell or animal. In another embodiment, the method is carried out in a cell free system.

In yet another embodiment, the polypeptide is further contacted with a substrate for the polypeptide, wherein the substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding agent. In one embodiment, the candidate compound is an inhibitor. In another embodiment, candidate compound is an activator.

In another aspect, the invention features a method of identifying a compound that modulates the transcriptional repression activity of the histone deacetylase polypeptide described above. The method comprises the steps of a) contacting the polypeptide with a candidate compound under conditions suitable for a transcriptional repression reaction; and b) assessing the transcriptional repression activity level of the polypeptide. A candidate compound that increases or decreases the transcriptional repression activity level of the polypeptide relative to a control is a compound that modulates the transcriptional repression activity of the polypeptide. In one embodiment, the method is carried out in a cell or animal. In another embodiment, the method is carried out in a cell free system.

In yet another embodiment, the polypeptide is further contacted with a substrate for the polypeptide, wherein the substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding agent. In one embodiment, the candidate compound is an inhibitor. In another embodiment, candidate compound is an activator.

In another aspect, the invention features a method of identifying a compound that modulates expression of a histone deacetylase nucleic acid molecule described above. The method comprises the steps of a) providing a nucleic acid molecule comprising a promoter region of the histone deacetylase nucleic acid molecule described above, or part of such a promoter region, operably linked to a reporter gene; b) contacting the nucleic acid molecule or with a candidate compound; and c) assessing the level of the reporter gene. A candidate compound that increases or decreases expression of the reporter gene relative to a control is a compound that modulates expression of the histone deacetylase nucleic acid molecule described above. In one embodiment, the method is carried out in a cell.

In still another aspect, the invention features a method of identifying a polypeptide that interacts with a histone deacetylase polypeptide described above in a yeast two-hybrid system. The method comprises the steps of a) providing a first nucleic acid vector comprising a nucleic acid molecule encoding a DNA binding domain and the histone deacetylase polypeptide described above; b) providing a second nucleic acid vector comprising a nucleic acid encoding a transcription

activation domain and a nucleic acid encoding a test polypeptide; c) contacting the first nucleic acid vector with the second nucleic acid vector in a yeast two-hybrid system; and d) assessing transcriptional activation in the yeast two-hybrid system. An increase in transcriptional activation relative to a control indicates that the test polypeptide is a polypeptide that interacts with the histone deacetylase polypeptide described above.

The invention also features a pharmaceutical composition comprising a histone deacetylase polypeptide described above.

In addition, the present invention features a method of diagnosing a cell proliferation disease, an apoptotic disease, or a cell differentiation disease in a subject. The method comprises the steps of a) obtaining a sample from the subject; and b) assessing the level of activity or expression of the histone deacetylase polypeptide described above or the level of the nucleic acid molecule described above in the sample. If the level is increased relative to a control, then the subject has an increased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and if the level is decreased relative to a control, then the subject has a decreased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In one embodiment, the polypeptide level is assayed using immunohistochemistry techniques. In another embodiment, the nucleic acid molecule level is assayed using *in situ* hybridization techniques.

Compounds and/or polypeptides identified in the above-described screening methods are also part of the present invention.

DESCRIPTION OF THE FIGURES

FIG. 1 is a schematic representation of the order in which FIGS. 1A-1O should be viewed.

FIGS. 1A-1C show the cDNA sequence of *HDAC9* (SEQ ID NO: 1). The arrows and numbers in the *HDAC9* sequence indicate exons. The boxed portion of the sequence indicates the HDAC domain.

FIGS. 1D-1G show the cDNA sequence of *HDAC9a* (SEQ ID NO: 3). The arrows and numbers in the *HDAC9a* sequence indicate exons. The boxed portion of the sequence indicates the HDAC domain.

FIGS. 1H-1I show the cDNA sequence of *HDRP(ΔNLS)* (SEQ ID NO:9).

FIGS. 1J-1L show the cDNA sequence of *HDAC9(ΔNLS)* (SEQ ID NO:5).

FIGS. 1M-1O show the cDNA sequence of *HDAC9a(ΔNLS)* (SEQ ID NO:7).

FIG. 2 is a schematic representation of the order in which FIGS. 2A-2E should be viewed.

FIG. 2A shows the amino acid sequence of HDAC9 (SEQ ID NO: 2).

FIG. 2B shows the amino acid sequence of HDAC9a (SEQ ID NO: 4).

FIG. 2C shows the amino acid sequence of HDAC9(ΔNLS) (SEQ ID NO: 6).

FIG. 2D shows the amino acid sequence of HDAC9a(ΔNLS) (SEQ ID NO: 8).

FIG. 2E shows the amino acid sequence of and HDRP(ΔNLS) (SEQ ID NO: 10).

FIG. 3 is a schematic representation of the order in which FIGS. 3A-3C should be viewed.

FIGS. 3A-3C show an amino acid sequence alignment of HDRP (SEQ ID NO: 11), HDAC9 (SEQ ID NO: 2), HDAC9a (SEQ ID NO: 4), and HDAC4 (SEQ ID NO: 12) polypeptides. Amino acid sequences of HDAC9 (GenBank Accession: AY032737; SEQ ID NO: 2) and HDAC9a (GenBank Accession:AY032738; SEQ ID NO: 4) are aligned with HDRP (GenBank Accession: BAA34464; SEQ D NO: 11) and HDAC4 (GenBank Accession: NP_006028; SEQ ID NO: 12). The identical residues in all proteins are boxed with solid lines. The similar residues are boxed with dotted lines.

FIG. 4 shows a schematic representation of the human *HDAC9* gene structure. The striped boxes represent exons present in isoforms HDRP, HDAC9a, and HDAC9. The lines represent introns. Broken lines are used for larger introns (with size in base pair on top). The 5' untranslated region cDNA and coding region cDNA are represented here. Exons 1-12 encode a non-catalytic domain of the

polypeptides, and exons 14-21 encode the histone deacetylase catalytic domain of the polypeptides, which provide the polypeptides with deacetylase activity.

FIG. 5 is a schematic representation of the order in which FIGS. 5A-5D should be viewed.

FIGS. 5A-5D show the nucleic acid sequence of *HDAC9*, containing all exons expressed in the various isoforms of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* of the present invention (SEQ ID NO:13).

FIG. 6A is a scanned imaged of a multiple human tissue Northern blot that was probed to determine mRNA expression of *HDAC9* using a cDNA probe that recognizes both *HDAC9* and *HDAC9a*. The tissues examined are lane 1, heart; lane 2, brain; lane 3, placenta; lane 4, lung; lane 5, liver; lane 6, skeletal muscle; lane 7, kidney; and lane 8, pancreas. Positions of the RNA size marker in kilobases (kb) are indicated to the left of the blot.

FIG. 6B is a scanned image of an electrophoretic gel showing the results of RT-PCR analyses of mRNA from the same tissues as examined in the Northern blot of FIG. 6A to determine the distribution of *HDAC9* and *HDAC9a* mRNA among these tissues. PCR products were resolved by agarose gel electrophoresis and visualized by ethidium bromide under UV light. A 1-kb DNA ladder was run on both sides of the gel with the size (in kb) indicated on the left. On the right side, the expected products for *HDAC9* and *HDAC9a* are indicated as 9 and 9a, respectively.

FIG. 7 is a graph of HDAC enzymatic activity of HDAC anti-FLAG-immunoprecipitated proteins isolated from vector control, HDAC9-FLAG, and HDAC9a-FLAG transfected 293T cells, as measured in fluorescence units using *FLUOR DE LYS*™ as a substrate in the presence or absence of 1 μM TSA. Results are shown as the mean of three independent assays. The inset is a scanned image of an anti-FLAG Western blot showing the amount of proteins used in the assay. V, Vector control; 9, HDAC9-FLAG; and 9a, HDAC9a-FLAG.

FIG. 8 is a graph of HDAC enzymatic activity of HDAC anti-FLAG-immunoprecipitated proteins isolated from vector control, and HDAC9a-FLAG (treated with 2 μM SAHA or left untreated) transfected 293T cells, as measured by ^{3}H-acetic acid released from ^{3}H-histones in the presence or absence of 2 μM SAHA.

Vector control; HDAC9a, HDAC9a-FLAG; and HDAC9a+, HDAC9a-FLAG + SAHA.

FIG. 9A shows a scanned image of a Western blot of 293T whole cell lysate and anti-FLAG immunoprecipitates from 293T cells transfected with vector, HDAC9-FLAG or HDAC9a-FLAG using antibodies against MEF2 and FLAG. Top panel, anti-MEF2 Western; bottom panel, anti-FLAG Western. L, 293T whole cell lysate; V, vector control IP; 9, HDAC9-FLAG IP; 9a, HDAC9a-FLAG IP.

FIG. 9B is a graph showing the transcription level of p3XMEF2-*Luc* in the presence or absence of pcDNA3 empty vector (-), pCMV-MEF2C, and/or a vector encoding pFLAG-HDAC9 or pFLAG-HDAC9a. p3XMEF2-*Luc* (100 ng) and pRL-TK (5 ng) were transfected into 293T cells with pcDNA3 empty vector (-) or with pCMV-MEF2C (100 ng) (+) along with the indicated amount of pFLAG-HDAC9 or pFLAG-HDAC9a. pFLAG empty vector was used to adjust the DNA to an equal amount in each transfection. The firefly luciferase activity was first normalized to the co-transfected Renilla luciferase activity and the value for MEF2C alone was then set as 1. Results are shown as the mean of three independent transfections +/- standard deviation.

FIG. 10 shows a schematic representation of the HDAC domains of human non-Sir2 family HDACs and HDRP. The boxes represent histone deacetylase (HDAC) domains.

FIG. 11 is a schematic representation of the order in which FIGS. 11A-11F should be viewed.

FIGS. 11A-11F show the nucleotide sequence of the vector pFLAG-CMV-5b-HDAC9 (VR1) (SEQ ID NO: 14). Lowercase letters are vector backbone, uppercase letters are HDAC9 sequence. "Acc" was added at the beginning of the HDAC9 sequence for translation initiation.

FIG. 12 is a schematic representation of the order in which FIGS. 12-1 through 12-66 should be viewed.

FIGS. 12-1 through 12-66 show the nucleotide sequence of the vector pFLAG-CMV-5b-HDAC9a (VR2), with restriction enzyme sites indicated (SEQ ID NO: 14).

FIG. 13 is a schematic representation of the order in which FIGS. 13A-13E should be viewed.

FIGS. 13A-13E show the nucleotide sequence of the vector pFLAG-CMV-5b-HDAC9a (VR2) (SEQ ID NO: 15). Lowercase letters are vector backbone, uppercase letters are HDAC9a sequence. "Acc" was added at the beginning of the HDAC9a sequence for translation initiation.

FIG. 14 is a schematic representation of the order in which FIGS. 14-1 through 14-61 should be viewed.

FIGS. 14-1 through 14-61 show the nucleotide sequence of the vector pFLAG-CMV-5b-HDAC9a (VR2), with restriction enzyme sites indicated (SEQ ID NO: 15).

DETAILED DESCRIPTION OF THE INVENTION

A protein designated HDRP (See Zhou *et al.*, Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)) (also called MITR (See Sparrow *et al.*, EMBO J. 18:5085-5098(1999); Zhang *et al.*, J. Biol. Chem., 276:35-39 (2001); and Zhang *et al.*, Proc. Natl. Acad. Sci. USA, 98:7354-7359 (2001)) that is 50% identical to the N-terminal domains of histone deacetylase 4 (HDAC4) and histone deacetylase 5 (HDAC5) was recently identified. The cloning and characterization of a novel histone deacetylase, *HDAC9*, of which HDRP is an alternatively spliced isoform is described herein. The cDNA sequence of *HDAC9* is shown in FIGS. 1A-1C (SEQ ID NO: 1), and the HDAC9 amino acid sequence is shown in FIG. 2A (SEQ ID NO: 2). In addition to cloning *HDAC9*, other alternatively spliced isoforms of HDAC9, designated as HDAC9a (a polypeptide that is 132 amino acids shorter at the C-terminal end than HDAC9), and isoforms of HDAC9, HDAC9a, and HDRP polypeptides that lack the nuclear localization signal (NLS) in the N-terminal non-catalytic end of HDAC9, termed HDAC9(ΔNLS), HDAC9a(ΔNLS), and HDRP(ΔNLS), respectively were also identified. The cDNA sequence of *HDAC9a* is shown in FIGS. 1D-1G (SEQ ID NO: 3), and the HDAC9a amino acid sequence is shown in FIG. 2B (SEQ ID NO: 4). The cDNA sequence of *HDAC9* lacking amino acids encoding an NLS (*HDAC9(ΔNLS)*) is shown in FIGS. 1J-1L (SEQ ID NO: 5), and the HDAC9 lacking an NLS amino acid sequence is shown in FIG. 2C (SEQ ID NO: 6). The cDNA

sequence of *HDAC9a* encoding a polypeptide lacking an NLS (*HDAC9a(ΔNLS)*) is shown in FIGS. 1M-1O (SEQ ID NO: 7), and the HDAC9a lacking an NLS amino acid sequence is shown in FIG. 2D (SEQ ID NO: 8). The cDNA sequence of *HDRP* encoding a polypeptide lacking an NLS (*HDRP(ΔNLS)*) is shown in FIGS. 1H-1I (SEQ ID NO: 9), and the HDRP lacking an NLS amino acid sequence is shown in FIG. 2E (SEQ ID NO: 10).

POLYPEPTIDES OF THE INVENTION

The present invention features isolated or recombinant HDAC9 polypeptides, HDAC9a polypeptides, HDAC9(ΔNLS) polypeptides, HDAC9a(ΔNLS) polypeptides, and HDRP(ΔNLS) polypeptides, and fragments, derivatives, and variants thereof, as well as polypeptides encoded by nucleotide sequences described herein (*e.g.*, other variants). As used herein, the term "polypeptide" refers to a polymer of amino acids, and not to a specific length; thus, peptides, oligopeptides, and proteins are included within the definition of a polypeptide.

As used herein, a polypeptide is said to be "isolated," "substantially pure," or "substantially pure and isolated" when it is substantially free of cellular material, when it is isolated from recombinant or non-recombinant cells, or free of chemical precursors or other chemicals when it is chemically synthesized. Typically, the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide is isolated, substantially pure, or substantially pure and isolated when it has a relative increased concentration or activity of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS), in comparison to total HDAC concentration or activity. Preferably the increased activity or concentration of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) is at least 2-fold, more preferably, at least 5-fold, and most preferably, at least 10 fold, in comparison to total HDAC concentration or activity. In addition, a polypeptide can be joined to another polypeptide with which it is not normally associated in a cell (*e.g.*, in a "fusion protein") and still be "isolated," "substantially pure," or "substantially pure and isolated." An isolated, substantially pure, or substantially pure and isolated polypeptide may be obtained, for example, using affinity

purification techniques described herein, as well as other techniques described herein and known to those skilled in the art.

By a "histone deacetylase polypeptide" is meant a polypeptide having histone deacetylase activity, transcription repression activity, and/or the ability to deacetylate other substrates, for example, transcription factors, including p53, CoRest, E2F, GATA-1, TFIIe, and TFIIF that normally have a nuclear or cytoplasmic location in a cell. A histone deacetylase polypeptide is also a polypeptide whose activity can be inhibited by molecules having HDAC inhibitory activity. These molecules fall into four general classes: 1) short-chain fatty acids (e.g., 4-phenylbutyrate and valproic acid); 2) hydroxamic acids(e.g. SAHA, Pyroxamide, trichostatin A (TSA), oxamflatin and CHAPs, such as, CHAP1 and CHAP 31); 3) cyclic tetrapeptides (Trapoxin A, Apicidin and Depsipeptide (FK-228, also known as FR9011228); 4) benzamides (e.g., MS-275); and other compounds such as Scriptaid. Examples of such compounds can be found in U.S. Patent Nos. 5,369,108, issued on November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, as well as, Yoshida *et al.*, Bioessays 17, 423-430 (1995), Saito *et al.*, PNAS USA 96, 4592-4597, (1999), Furamai *et al.*, PNAS USA 98 (1), 87-92 (2001), Komatsu *et al.*, Cancer Res. 61(11), 4459-4466 (2001), Su *et al.*, Cancer Res. 60, 3137-3142 (2000), Lee *et al.*, Cancer Res. 61(3), 931-934 and Suzuki *et al.* J. Med. Chem. 42(15), 3001-3003 (1999) the entire content of all of which are hereby incorporated by reference. Examples of such histone deacetylase polypeptides include HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), HDRP(ΔNLS); a substantially pure polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and a polypeptide having preferably at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, as determined using the BLAST program and parameters described herein.

In one embodiment, the histone deacetylase polypeptide has histone deacetylase activity, transcription repression activity, the ability to deacetylate substrates, or is inhibited by trichostatin A or a hybrid polar compound such as

SAHA. In another embodiment, the HDAC9(ΔNLS) polypeptide has any two of the above biological activities. In still another embodiment, the HDAC9(ΔNLS) polypeptide has any three of the above biological activities. In yet another embodiment, the HDAC9(ΔNLS) polypeptide has all of the above biological activities.

An HDAC9 polypeptide is a histone deacetylase polypeptide as described above. An HDAC9 polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 2, as determined using the BLAST program and parameters described herein. An HDAC9 polypeptide is also a polypeptide that comprises the amino acids encoded by exons 23, 24, 25 and/or 26, and that does not comprise the amino acids encoded by exon 13 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1A-1C, FIG. 4, and FIGS. 5A-5D. Preferably, an HDAC9 polypeptide comprises the sequence of SEQ ID NO: 2. More preferably, an HDAC9 polypeptide consists of the sequence of SEQ ID NO: 2. An HDAC polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 1.

An HDAC9a polypeptide is a histone deacetylase polypeptide as described above. An HDAC9a polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 4, as determined using the BLAST program and parameters described herein. An HDAC9a polypeptide is also a polypeptide that comprises the amino acids encoded by exon 22, and that does not comprise the amino acids encoded by exons 13, 23, 24, 25, or 26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1D-1G, FIG. 4, and FIGS. 5A-5D. Preferably, an HDAC9a polypeptide comprises the sequence of SEQ ID NO: 4. More preferably, an HDAC9a polypeptide consists of the sequence of SEQ ID NO: 4. An HDAC9a polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 3.

An HDAC9(ΔNLS) is a histone deacetylase polypeptide as described above. An HDAC9(ΔNLS) polypeptide does not comprise a nuclear localization signal (NLS). An HDAC9(ΔNLS) polypeptide preferably has at least 60%, more

preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 6, as determined using the BLAST program and parameters described herein. An HDAC9(ΔNLS) polypeptide is also a polypeptide that comprises the amino acids encoded by exons 23, 24, 25, and/or 26, and that does not comprise the amino acids encoded by exons 7 or 13 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1J-1L, and FIGS. 5A-5D. Preferably, an HDAC9(ΔNLS) polypeptide comprises the sequence of SEQ ID NO: 6. More preferably, an HDAC9(ΔNLS) polypeptide consists of the sequence of SEQ ID NO: 6. An HDAC9(ΔNLS) polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 5.

An HDAC9a(ΔNLS) polypeptide is a histone deacetylase polypeptide as described above. An HDAC9a(ΔNLS) does not comprise a nuclear localization signal (NLS). An HDAC9a(ΔNLS) polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 8, as determined using the BLAST program and parameters described herein. An HDAC9a(ΔNLS) polypeptide is also a polypeptide that comprises the amino acids encoded by exon 22, and that does not comprise the amino acids encoded by exons 7, 13, 23, 24, 25, or 26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1M-1O, and FIGS. 5A-5D. Preferably, an HDAC9a(ΔNLS) polypeptide comprises the sequence of SEQ ID NO: 8. More preferably, an HDAC9a(ΔNLS) polypeptide consists of the sequence of SEQ ID NO: 8. An HDAC9a(ΔNLS) polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 7.

An HDRP(ΔNLS) polypeptide is a histone deacetylase polypeptide as described above. An HDRP(ΔNLS) does not comprise a nuclear localization signal (NLS). An HDRP(ΔNLS) polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 10, as determined using the BLAST program and parameters described herein. An HDRP(ΔNLS) polypeptide is also a polypeptide that does not comprise the amino acids encoded by exons 7 or 13-26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1H-1I and FIGS. 5A-5D. Preferably, an HDRP(ΔNLS) polypeptide comprises the sequence of SEQ ID NO: 10. More preferably, an

HDRP(ΔNLS) polypeptide consists of the sequence of SEQ ID NO: 10. An HDRP(ΔNLS) polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 9.

The polypeptides of the invention can be purified to homogeneity. It is understood, however, that preparations in which the polypeptide is not purified to homogeneity are useful. The critical feature is that the preparation allows for the desired function of the polypeptide, even in the presence of considerable amounts of other components. Thus, the invention encompasses various degrees of purity. In one embodiment, the language "substantially free of cellular material" includes preparations of the polypeptide having less than about 30% (by dry weight) other proteins (*i.e.*, contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins.

When a polypeptide is recombinantly produced, it can also be substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, less than about 10%, or less than about 5% of the volume of the polypeptide preparation. The language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

In one embodiment, a polypeptide of the invention comprises an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and complements and portions thereof, (*e.g.*, a complement of any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 or a portion of any one of SEQ ID NO: 1 or SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9).

The polypeptides of the invention also encompass fragments and sequence variants. Variants include a substantially homologous polypeptide encoded by the

same genetic locus in an organism, *i.e.*, an allelic variant, as well as other variants. Variants also encompass polypeptides derived from other genetic loci in an organism, but having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and complements and portions thereof, or having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of nucleotide sequences encoding any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. Variants also include polypeptides substantially homologous or identical to these polypeptides but derived from another organism, *i.e.*, an ortholog. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by chemical synthesis. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by recombinant methods.

As used herein, two polypeptides (or a region of the polypeptides) are substantially homologous or identical when the amino acid sequences are at least about 60-65%, typically at least about 70-75%, more typically at least about 80-85%, and most typically greater than about 90-95% or more homologous or identical. A substantially identical or homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid molecule hybridizing to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a portion thereof, under stringent conditions as more particularly described herein, or will be encoded by a nucleic acid molecule hybridizing to a nucleic acid sequence encoding SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or portion thereof, under stringent conditions as more particularly described herein.

The percent identity of two nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first sequence). The nucleotides or amino acids at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions x 100). In

certain embodiments, the length of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), and HDRP(ΔNLS) amino acid or nucleotide sequence aligned for comparison purposes is at least 30%, preferably, at least 40%, more preferably, at least 60%, and even more preferably, at least 70%, 80%, 90%, or 100% of the length of the reference sequence, for example, those sequences provided in FIGS. 1A-1O and 2A-2E. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A preferred, non-limiting example of such a mathematical algorithm is described in Karlin *et al.*, Proc. Natl. Acad. Sci. USA, 90:5873-5877 (1993). Such an algorithm is incorporated into the BLASTN and BLASTX programs (version 2.2) as described in Schaffer *et al.*, Nucleic Acids Res., 29:2994-3005 (2001). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, BLASTN) can be used. See http://www.ncbi.nlm.nih.gov, as available on August 10, 2001. In one embodiment, the database searched is a non-redundant (NR) database, and parameters for sequence comparison can be set at: no filters; Expect value of 10; Word Size of 3; the Matrix is BLOSUM62; and Gap Costs have an Existence of 11 and an Extension of 1.

Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0), which is part of the GCG (Accelrys) sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12 , and a gap penalty of 4 can be used. Additional algorithms for sequence analysis are known in the art and include ADVANCE and ADAM as described in Torellis and Robotti, Comput. Appl. Biosci., 10: 3-5 (1994); and FASTA described in Pearson and Lipman, Proc. Natl. Acad. Sci USA, 85: 2444-8 (1988).

In another embodiment, the percent identity between two amino acid sequences can be accomplished using the GAP program in the GCG software package (available at http://www.accelrys.com, as available on August 31, 2001) using either a Blossom 63 matrix or a PAM250 matrix, and a gap weight of 12, 10, 8, 6, or 4 and a length weight of 2, 3, or 4. In yet another embodiment, the percent

identity between two nucleic acid sequences can be accomplished using the GAP program in the GCG software package (available at http://www.cgc.com), using a gap weight of 50 and a length weight of 3.

The invention also encompasses HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9aΔNLS, and HDRP(ΔNLS) polypeptides having a lower degree of identity but having sufficient similarity so as to perform one or more of the same functions performed by an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9aΔNLS, or HDRP(ΔNLS) polypeptide encoded by a nucleic acid molecule of the invention. Similarity is determined by conserved amino acid substitution. Such substitutions are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Conservative substitutions are likely to be phenotypically silent. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu, and Ile; interchange of the hydroxyl residues Ser and Thr; exchange of the acidic residues Asp and Glu; substitution between the amide residues Asn and Gln; exchange of the basic residues Lys and Arg; and replacements among the aromatic residues Phe and Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent are found in Bowie *et al.*, Science 247: 1306-1310 (1990).

A variant polypeptide can differ in amino acid sequence by one or more substitutions, deletions, insertions, inversions, fusions, and truncations or a combination of any of these. Further, variant polypeptides can be fully functional or can lack function in one or more activities, for example, in histone deacetylase activity or transcription repression activity. Fully functional variants typically contain only conservative variation or variation in non-critical residues or in non-critical regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree. Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncations or a substitution, insertion, inversion, or deletion in a critical residue or critical region, such critical regions include the HDAC domains, which provide the polypeptide

with deacetylase activity, as shown in the nucleic acid sequences of FIGS. 1A-1G, as well as in the schematic of FIG. 4.

Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham *et al.*, Science, 244: 1081-1085 (1989)). The latter procedure introduces a single alanine mutation at each of the residues in the molecule (one mutation per molecule). The resulting mutant molecules are then tested for biological activity *in vitro*. Sites that are critical for polypeptide activity can also be determined by structural analysis, such as crystallization, nuclear magnetic resonance, or photoaffinity labeling (See Smith *et al.*, J. Mol. Biol., 224: 899-904 (1992); and de Vos *et al.* Science, 255: 306-312 (1992)).

The invention also includes HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), and HDRP(ΔNLS) polypeptide fragments of the polypeptides of the invention. Fragments can be derived from a polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or from a polypeptide encoded by a nucleic acid molecule comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 or a portion thereof and the complements thereof or other variants. The present invention also encompasses fragments of the variants of the polypeptides described herein. Useful fragments include those that retain one or more of the biological activities of the polypeptide as well as fragments that can be used as an immunogen to generate polypeptide-specific antibodies.

Biologically active fragments (peptides that are, for example, 6, 9, 12, 15, 16, 20, 30, 35, 36, 37, 38, 39, 40, 50, 100, or more amino acids in length) can comprise a domain, segment, or motif, for example, an HDAC domain, that has been identified by analysis of the polypeptide sequence using well-known methods, *e.g.*, signal peptides, extracellular domains, one or more transmembrane segments or loops, ligand binding regions, zinc finger domains, DNA binding domains, acylation sites, glycosylation sites, or phosphorylation sites.

Fragments can be discrete (not fused to other amino acids or polypeptides) or can be within a larger polypeptide. Further, several fragments can be comprised within a single larger polypeptide. In one embodiment a fragment designed for

expression in a host can have heterologous pre- and pro-polypeptide regions fused to the amino terminus of the polypeptide fragment and an additional region fused to the carboxyl terminus of the fragment.

The invention thus provides chimeric or fusion polypeptides. These comprise an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9aΔNLS, or HDRP(ΔNLS) polypeptide of the invention operatively linked to a heterologous protein or polypeptide having an amino acid sequence not substantially homologous to the polypeptide. "Operatively linked" indicates that the polypeptide and the heterologous protein are fused in-frame. The heterologous protein can be fused to the N-terminus or C-terminus of the polypeptide. In one embodiment, the fusion polypeptide does not affect the function of the polypeptide per se. For example, the fusion polypeptide can be a GST-fusion polypeptide in which the polypeptide sequences are fused to the C-terminus of the GST sequences. Other types of fusion polypeptides include, but are not limited to, enzymatic fusion polypeptides, for example, β-galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions, and Ig fusions. Such fusion polypeptides, particularly poly-His fusions, can facilitate the purification of recombinant polypeptide. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of a polypeptide can be increased by using a heterologous signal sequence. Therefore, in another embodiment, the fusion polypeptide contains a heterologous signal sequence at its N-terminus.

EP-A 0464 533 discloses fusion proteins comprising various portions of immunoglobulin constant regions. The Fc is useful in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262). In drug discovery, for example, human proteins have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists. (See Bennett *et al.*, Journal of Molecular Recognition, 8: 52-58 (1995) and Johanson *et al.*, The Journal of Biological Chemistry, 270,16: 9459-9471 (1995)). Thus, this invention also encompasses soluble fusion polypeptides containing a polypeptide of the invention and various portions of the constant regions of heavy or light chains of immunoglobulins of various subclass (IgG, IgM, IgA, IgE).

A chimeric or fusion polypeptide can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of nucleic acid fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive nucleic acid fragments that can subsequently be annealed and re-amplified to generate a chimeric nucleic acid sequence (see Ausubel *et al.*, "Current Protocols in Molecular Biology," John Wiley & Sons, (1998), the entire teachings of which are incorporated by reference herein). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST protein). A nucleic acid molecule encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide.

The substantially pure, isolated, or substantially pure and isolated HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9aΔNLS, or HDRP(ΔNLS) polypeptide can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. In one embodiment, the polypeptide is produced by recombinant DNA techniques. For example, a nucleic acid molecule encoding the polypeptide is cloned into an expression vector, the expression vector introduced into a host cell, and the polypeptide expressed in the host cell. The polypeptide can then be isolated from the cells by an appropriate purification scheme using standard protein purification techniques.

In general, HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9aΔNLS, and HDRP(ΔNLS) polypeptides of the present invention can be used as a molecular weight marker on SDS-PAGE gels or on molecular sieve gel filtration columns using art-recognized methods. The polypeptides of the present invention can be used to raise antibodies or to elicit an immune response. The polypeptides can also be used as a reagent, *e.g.*, a labeled reagent, in assays to quantitatively determine levels of the polypeptide or a molecule to which it binds (*e.g.*, a receptor or a ligand) in biological fluids. The polypeptides can also be used as markers for cells or tissues

in which the corresponding polypeptide is preferentially expressed, either constitutively, during tissue differentiation, or in a diseased state. The polypeptides can be used to isolate a corresponding binding agent, and to screen for peptide or small molecule antagonists or agonists of the binding interaction. The polypeptides of the present invention can also be used as therapeutic agents.

NUCLEIC ACID MOLECULES OF THE INVENTION

The present invention also features isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules.

By a "histone deacetylase nucleic acid molecule" is meant a nucleic acid molecule that encodes a histone deacetylase polypeptide. Such histone nucleic acids include, for example, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule described in detail herein; an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, or SEQ ID NO: 7; and an isolated nucleic acid molecule that has at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof.

An *HDAC9* nucleic acid molecule is a nucleic acid molecule that encodes an HDAC9 polypeptide. In one embodiment, the *HDAC9* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 1; a complement of an isolated nucleic acid comprising SEQ ID NO: 1;

an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2; a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 2; a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 1, as determined using the BLAST program and parameters described herein. In another embodiment, the *HDAC9* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 1.

An *HDAC9a* nucleic acid molecule is a nucleic acid molecule that encodes an HDAC9a polypeptide. An *HDAC9a* nucleic acid molecule preferably has at least 55%, sequence identity to SEQ ID NO: 3, In one embodiment, the *HDAC9a* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 3; a complement of an isolated nucleic acid comprising SEQ ID NO: 3; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 4; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 4; a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 4; a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 3; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 3 or a complement thereof, as determined using the BLAST program and parameters described herein. In another embodiment, the *HDAC9a* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 3.

An *HDAC9(ΔNLS)* nucleic acid molecule is a nucleic acid molecule that encodes an HDAC9(ΔNLS) polypeptide. In one embodiment, the *HDAC9(ΔNLS)* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 5; a complement of an isolated nucleic acid comprising SEQ ID NO: 5; an isolated nucleic acid encoding a histone deacetylase

polypeptide of SEQ ID NO: 6; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 6; a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 6; a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 5; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 5 or a complement thereof, as determined using the BLAST program and parameters described herein. In another embodiment, the *HDAC9(ΔNLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 5.

An *HDAC9a(ΔNLS)* nucleic acid molecule is a nucleic acid molecule that encodes an HDAC9a(ΔNLS) polypeptide. In one embodiment, the *HDAC9a(ΔNLS)* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 7; a complement of an isolated nucleic acid comprising SEQ ID NO: 7; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 8; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 8; a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 8; a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 7; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 7 or a complement thereof, as determined using the BLAST program and parameters described herein. In another embodiment, the *HDAC9a(ΔNLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 7.

An "*HDRP(ΔNLS)* nucleic acid molecule" is a nucleic acid molecule that encodes an HDRP(ΔNLS) polypeptide. In one embodiment, the *HDRP(ΔNLS)* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 9; a complement of an isolated nucleic acid comprising SEQ ID NO: 9; an isolated nucleic acid encoding a histone deacetylase

polypeptide of SEQ ID NO: 10; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 10; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 9 or a complement thereof, as determined using the BLAST program and parameters described herein.. In another embodiment, the *HDRP(ΔNLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 9.

The isolated nucleic acid molecules of the present invention can be RNA, for example, mRNA, or DNA, such as cDNA and genomic DNA. DNA molecules can be double-stranded or single-stranded; single stranded RNA or DNA can be either the coding, or sense, strand or the non-coding, or antisense, strand. The nucleic acid molecule can include all or a portion of the coding sequence of the gene and can further comprise additional non-coding sequences such as introns and non-coding 3' and 5' sequences (including regulatory sequences, for example). Additionally, the nucleic acid molecule can be fused to a marker sequence, for example, a sequence that encodes a polypeptide to assist in isolation or purification of the polypeptide. Such sequences include, but are not limited to, those that encode a glutathione-S-transferase (GST) fusion protein and those that encode a hemagglutinin A (HA) polypeptide marker from influenza.

An "isolated," "substantially pure," or "substantially pure and isolated" nucleic acid molecule, as used herein, is one that is separated from nucleic acids that normally flank the gene or nucleotide sequence (as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (*e.g.*, as in an RNA or cDNA library). For example, an isolated nucleic acid of the invention may be substantially isolated with respect to the complex cellular milieu in which it naturally occurs, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. In some instances, the isolated material will form part of a composition (for example, a crude extract containing other substances), buffer system, or reagent mix. In other circumstances, the material may be purified to essential homogeneity, for example, as determined by agarose gel electrophoresis or column chromatography such as

HPLC. Preferably, an isolated nucleic acid molecule comprises at least about 50, 80, or 90% (on a molar basis) of all macromolecular species present.

With regard to genomic DNA, the term "isolated" also can refer to nucleic acid molecules that are separated from the chromosome with which the genomic DNA is naturally associated. For example, the isolated nucleic acid molecule can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb, or 0.1 kb of nucleotides that flank the nucleic acid molecule in the genomic DNA of the cell from which the nucleic acid molecule is derived.

The *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated. Thus, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleic acid molecules include recombinant DNA molecules in heterologous host cells, as well as partially or substantially purified DNA molecules in solution. "Isolated" nucleic acid molecules also encompass *in vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention. An isolated nucleic acid molecule or nucleotide sequence can include a nucleic acid molecule or nucleotide sequence that is synthesized chemically or by recombinant means. Therefore, recombinant DNA contained in a vector are included in the definition of "isolated" as used herein.

Isolated nucleotide molecules also include recombinant DNA molecules in heterologous organisms, as well as partially or substantially purified DNA molecules in solution. *In vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention are also encompassed by "isolated" nucleotide sequences. Such isolated nucleotide sequences are useful in the manufacture of the encoded polypeptide, as probes for isolating homologous sequences (*e.g.*, from other mammalian species), for gene mapping (*e.g.*, by *in situ* hybridization with chromosomes), or for detecting expression of the gene in tissue (*e.g.*, human tissue), such as by Northern blot analysis.

The present invention also pertains to variant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that are not necessarily found in nature but that encode an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide. Thus, for

example, DNA molecules that comprise a sequence that is different from the naturally-occurring *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleotide sequence but which, due to the degeneracy of the genetic code, encode an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide of the present invention are also the subject of this invention.

The invention also encompasses *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleotide sequences encoding portions (fragments), or encoding variant polypeptides such as analogues or derivatives of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide. Such variants can be naturally-occurring, such as in the case of allelic variation or single nucleotide polymorphisms, or non-naturally-occurring, such as those induced by various mutagens and mutagenic processes. Intended variations include, but are not limited to, addition, deletion, and substitution of one or more nucleotides that can result in conservative or non-conservative amino acid changes, including additions and deletions. Preferably, the *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS)* nucleotide (and/or resultant amino acid) changes are silent or conserved; that is, they do not alter the characteristics or activity of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide. In one preferred embodiment, the nucleotide sequences are fragments that comprise one or more polymorphic microsatellite markers.

Other alterations of the *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecules of the invention can include, for example, labeling, methylation, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, and carbamates), charged linkages (*e.g.*, phosphorothioates or phosphorodithioates), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine or psoralen), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids). Also included are synthetic molecules that mimic nucleic acid molecules in the ability to bind to a designated sequences via hydrogen bonding and other chemical

interactions. Such molecules include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The invention also pertains to *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that hybridize under high stringency hybridization conditions, such as for selective hybridization, to a nucleotide sequence described herein (*e.g.*, nucleic acid molecules that specifically hybridize to a nucleotide sequence encoding polypeptides described herein, and, optionally, have an activity of the polypeptide). In one embodiment, the invention includes variants described herein that hybridize under high stringency hybridization conditions (*e.g.*, for selective hybridization) to a nucleotide sequence comprising a nucleotide sequence selected from SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and the complement of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ D NO: 7, or SEQ ID NO: 9. In another embodiment, the invention includes variants described herein that hybridize under high stringency hybridization conditions (*e.g.*, for selective hybridization) to a nucleotide sequence encoding an amino acid sequence of SEQ ID NO: 2 (HDAC9), SEQ ID NO: 4 (HDAC9a), SEQ ID NO: 6 (HDAC9(ΔNLS)), SEQ ID NO: 8 (HDAC9a(ΔNLS)), or SEQ ID NO: 10 (HDRP(ΔNLS)). In a preferred embodiment, the variant that hybridizes under high stringency hybridizations encodes a polypeptide that has a biological activity of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide (*e.g.*, histone deacetylase activity or transcription repression activity).

Such nucleic acid molecules can be detected and/or isolated by specific hybridization (*e.g.*, under high stringency conditions). "Specific hybridization," as used herein, refers to the ability of a first nucleic acid to hybridize to a second nucleic acid in a manner such that the first nucleic acid does not hybridize to any nucleic acid other than to the second nucleic acid (*e.g.*, when the first nucleic acid has a higher similarity to the second nucleic acid than to any other nucleic acid in a sample wherein the hybridization is to be performed). "Stringency conditions" for hybridization is a term of art that refers to the incubation and wash conditions, *e.g.*, conditions of temperature and buffer concentration, that permit hybridization of a particular nucleic acid to a second nucleic acid; the first nucleic acid may be

perfectly (*i.e.*, 100%) complementary to the second, or the first and second may share some degree of complementarity that is less than perfect (*e.g.*, 70%, 75%, 85%, 95%). For example, certain high stringency conditions can be used that distinguish perfectly complementary nucleic acids from those of less complementarity. "High stringency conditions," "moderate stringency conditions," and "low stringency conditions" for nucleic acid hybridizations are explained on pages 2.10.1-2.10.16 and pages 6.3.1-6.3.6 in Current Protocols in Molecular Biology (See Ausubel *et al., supra*, the entire teachings of which are incorporated by reference herein). The exact conditions that determine the stringency of hybridization depend not only on ionic strength (*e.g.*, 0.2XSSC or 0.1XSSC), temperature (*e.g.*, room temperature, 42°C or 68°C), and the concentration of destabilizing agents such as formamide or denaturing agents such as SDS, but also on factors such as the length of the nucleic acid sequence, base composition, percent mismatch between hybridizing sequences, and the frequency of occurrence of subsets of that sequence within other non-identical sequences. Thus, equivalent conditions can be determined by varying one or more of these parameters while maintaining a similar degree of identity or similarity between the two nucleic acid molecules. Typically, conditions are used such that sequences at least about 60%, at least about 70%, at least about 80%, at least about 90% or at least about 95% or more identical to each other remain hybridized to one another. By varying hybridization conditions from a level of stringency at which no hybridization occurs to a level at which hybridization is first observed, conditions that will allow a given sequence to hybridize (*e.g.*, selectively) with the most similar sequences in the sample can be determined.

Exemplary conditions are described in Krause and Aaronson, Methods in Enzymology, 200:546-556 (1991). Also, in, Ausubel, *et al., supra*, which describes the determination of washing conditions for moderate or low stringency conditions. Washing is the step in which conditions are usually set so as to determine a minimum level of complementarity of the hybrids. Generally, starting from the lowest temperature at which only homologous hybridization occurs, each °C by which the final wash temperature is reduced (holding SSC concentration constant) allows an increase by 1% in the maximum extent of mismatching among the

sequences that hybridize. Generally, doubling the concentration of SSC results in an increase in Tm of 17°C. Using these guidelines, the washing temperature can be determined empirically for high, moderate, or low stringency, depending on the level of mismatch sought.

For example, a low stringency wash can comprise washing in a solution containing 0.2XSSC/0.1% SDS for 10 minutes at room temperature; a moderate stringency wash can comprise washing in a prewarmed solution (42°C) solution containing 0.2XSSC/0.1% SDS for 15 minutes at 42°C; and a high stringency wash can comprise washing in prewarmed (68°C) solution containing 0.1XSSC/0.1%SDS for 15 minutes at 68°C. Furthermore, washes can be performed repeatedly or sequentially to obtain a desired result as known in the art. Equivalent conditions can be determined by varying one or more of the parameters given as an example, as known in the art, while maintaining a similar degree of identity or similarity between the target nucleic acid molecule and the primer or probe used.

To determine the percent homology or identity of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of one polypeptide or nucleic acid molecule for optimal alignment with the other polypeptide or nucleic acid molecule). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared, as described above.

The present invention also provides isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleotide sequence comprising a nucleotide sequence selected from SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 and also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleotide sequence encoding an amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, and SEQ ID NO: 10. The nucleic acid fragments of the invention are at least about 15, preferably, at least about 18, 20, 23, or 25 nucleotides, and can be 30, 40, 50, 100, 200 or more nucleotides in length. Longer

fragments, for example, 30 or more nucleotides in length, that encode antigenic polypeptides described herein are particularly useful, such as for the generation of antibodies as described above.

In a related aspect, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid fragments of the invention are used as probes or primers in assays such as those described herein. "Probes" or "primers" are oligonucleotides that hybridize in a base-specific manner to a complementary strand of nucleic acid molecules. Such probes and primers include polypeptide nucleic acids, as described in Nielsen *et al.*, Science, 254, 1497-1500 (1991). As also used herein, the term "primer" in particular refers to a single-stranded oligonucleotide that acts as a point of initiation of template-directed DNA synthesis using well-known methods (*e.g.*, PCR, LCR) including, but not limited to those described herein.

Typically, a probe or primer comprises a region of nucleotide sequence that hybridizes to at least about 15, typically about 20-25, and more typically about 40, 50 or 75, consecutive nucleotides of a nucleic acid molecule comprising a contiguous nucleotide sequence selected from: SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and a sequence encoding an amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.

In preferred embodiments, a probe or primer comprises 100 or fewer nucleotides, preferably, from 6 to 50 nucleotides, and more preferably, from 12 to 30 nucleotides. In other embodiments, the probe or primer is at least 70% identical to the contiguous nucleotide sequence or to the complement of the contiguous nucleotide sequence, preferably, at least 80% identical, more preferably, at least 90% identical, even more preferably, at least 95% identical, or even capable of selectively hybridizing to the contiguous nucleotide sequence or to the complement of the contiguous nucleotide sequence. Often, the probe or primer further comprises a label, *e.g.*, radioisotope, fluorescent compound, enzyme, or enzyme co-factor.

The nucleic acid molecules of the invention such as those described above can be identified and isolated using standard molecular biology techniques and the sequence information provided in SEQ ID NO: 1, SEQ ID NO; 3, SEQ ID NO: 5,

SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, and /or SEQ ID NO: 10. For example, nucleic acid molecules can be amplified and isolated by the polymerase chain reaction using synthetic oligonucleotide primers designed based on one or more of the nucleic acid sequences provided above and/or the complement of those sequences. Or such nucleic acid molecules may be designed based on nucleotide sequences encoding one or more of the amino acid sequences provided in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. See generally PCR Technology: Principles and Applications for DNA Amplification (ed. H.A. Erlich, Freeman Press, NY, NY, (1992); PCR Protocols: A Guide to Methods and Applications (Eds. Innis *et al.*, Academic Press, San Diego, CA, (1990); Mattila *et al.*, Nucleic Acids Res., 19: 4967 (1991); Eckert *et al.*, PCR Methods and Applications, 1: 17 (1991); PCR (eds. McPherson *et al.*, IRL Press, Oxford)); and U.S. Patent No. 4,683,202. The nucleic acid molecules can be amplified using cDNA, mRNA, or genomic DNA as a template, cloned into an appropriate vector and characterized by DNA sequence analysis.

Other suitable amplification methods include the ligase chain reaction (LCR) (See Wu and Wallace, Genomics, 4:560 (1989), Landegren *et al.*, Science, 241:1077 (1988)), transcription amplification (Kwoh *et al.*, Proc. Natl. Acad. Sci. USA, 86:1173 (1989)), and self-sustained sequence replication (See Guatelli *et al.*, Proc. Nat. Acad. Sci. USA, 87:1874 (1990)) and nucleic acid based sequence amplification (NASBA). The latter two amplification methods involve isothermal reactions based on isothermal transcription, that produce both single stranded RNA (ssRNA) and double stranded DNA (dsDNA) as the amplification products in a ratio of about 30 or 100 to 1, respectively.

The amplified DNA can be radiolabeled and used as a probe for screening a cDNA library derived from human cells, mRNA in zap express, ZIPLOX, or other suitable vector. Corresponding clones can be isolated, DNA can be obtained following *in vivo* excision, and the cloned insert can be sequenced in either or both orientations by art-recognized methods to identify the correct reading frame encoding a polypeptide of the appropriate molecular weight. For example, the direct analysis of the nucleotide sequence of nucleic acid molecules of the present

invention can be accomplished using well-known methods that are commercially available. See, for example, Sambrook *et al.*, Molecular Cloning, A Laboratory Manual (2nd Ed., CSHP, New York (1989)); Zyskind *et al.*, Recombinant DNA Laboratory Manual, (Acad. Press, (1988)). Using these or similar methods, the polypeptide and the DNA encoding the polypeptide can be isolated, sequenced, and further characterized.

Antisense nucleic acid molecules of the invention can be designed using the nucleotide sequences of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and/or the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and/or a portion of those sequences, and/or the complement of those portion or sequences, and/or a sequence encoding the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or encoding a portion of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. Such antisense nucleic acid molecules can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid molecule (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Alternatively, the antisense nucleic acid molecule can be produced biologically using an expression vector into which a nucleic acid molecule has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid molecule will be of an antisense orientation to a target nucleic acid of interest).

In general, the isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid sequences of the invention can be used as molecular weight markers on Southern blots, and as chromosome markers that are labeled to map related gene positions. The nucleic acid sequences can also be used to compare with endogenous DNA sequences in patients to identify genetic disorders (*e.g.*, a predisposition for or susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease), and as probes, such as to hybridize and

discover related DNA sequences or to subtract out known sequences from a sample. The nucleic acid molecules of the present invention can also be used as therapeutic agents.

By a "cell proliferation disease" is meant a disease that is caused by or results in undesirably high levels of cell division, undesirably low levels of apoptosis, or both. For example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer are all examples of cell proliferation diseases. Myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, and chronic myelogenous leukemia are also cell proliferation diseases.

By a "cell differentiation disease" is meant a disease that is caused by or results in undesirably low levels of cell differentiation, or by undesirably high levels of cell differentiation. For example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer are all examples of cell differentiation diseases. Myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, and chronic myelogenous leukemia are also cell differentiation diseases.

By an "apoptotic disease" is meant a condition in which the apoptotic response is abnormal. This may pertain to a cell or a population of cells that does not undergo cell death under appropriate conditions. For example, normally a cell will die upon exposure to apoptotic-triggering agents, such as chemotherapeutic agents, or ionizing radiation. When, however, a subject has an apoptotic disease, for example, cancer, the cell or a population of cells may not undergo cell death in response to contact with apoptotic-triggering agents. In addition, a subject may have an apoptotic disease when the occurrence of cell death is too low, for example, when the number of proliferating cells exceeds the number of cells undergoing cell death, as occurs in cancer when such cells do not properly differentiate.

An apoptotic disease may also be a condition characterized by the occurrence of undesirably high levels of apoptosis. For example, certain neurodegenerative diseases, including but not limited to Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, restenosis, stroke, and ischemic

brain injury are apoptotic diseases in which neuronal cells undergo undesired cell death.

Other diseases for which the polypeptides and nucleic acid molecules of the present invention may be useful for diagnosing and/or treating include, but are not limited to Huntington's disease.

The *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules of the present invention can further be used to derive primers for genetic fingerprinting, to raise anti-polypeptide antibodies using DNA immunization techniques, and as an antigen to raise anti-DNA antibodies or elicit immune responses. Portions or fragments of the nucleotide sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample.

In addition, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleotide sequences of the invention can be used to identify and express recombinant polypeptides for analysis, characterization, or therapeutic use, or as markers for tissues in which the corresponding polypeptide is expressed, either constitutively, during tissue differentiation, or in diseased states. The nucleic acid sequences can additionally be used as reagents in the screening and/or diagnostic assays described herein, and can also be included as components of kits (*e.g.*, reagent kits) for use in the screening and/or diagnostic assays described herein.

Standard techniques, such as the polymerase chain reaction (PCR) and DNA hybridization, may be used to clone *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* homologs in other species, for example, mammalian homologs. *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* homologs may be readily identified using low-stringency DNA hybridization or low-stringency PCR with human *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* probes or primers. Degenerate primers encoding human HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or

HDRP(ΔNLS) polypeptides may be used to clone *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* homologs by RT-PCR.

Alternatively, additional *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* homologs can be identified by utilizing consensus sequence information for HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptides to search for similar polypeptides in other species. For example, polypeptide databases for other species can be searched for proteins with the HDAC domains described herein. Candidate polypeptides containing such a motif can then be tested for their HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) biological activities, using methods described herein.

EXPRESSION OF THE NUCLEIC ACID MOLECULES OF THE INVENTION

Another aspect of the invention pertains to nucleic acid constructs containing an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule, for example, one selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 (or portions thereof). Yet another aspect of the invention pertains to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid constructs containing a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. The constructs comprise a vector (*e.g.*, an expression vector) into which a sequence of the invention has been inserted in a sense or antisense orientation.

As used herein, the term "vector" or "construct" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal

mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses) that serve equivalent functions.

Preferred recombinant expression vectors of the invention comprise a nucleic acid molecule of the invention in a form suitable for expression of the nucleic acid molecule in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences).

It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed and the level of expression of polypeptide desired. The expression vectors of the invention can be introduced into host cells to thereby produce polypeptides, including fusion polypeptides, encoded by nucleic acid molecules as described herein.

The recombinant expression vectors of the invention can be designed for expression of a polypeptide of the invention in prokaryotic or eukaryotic cells, *e.g.*, bacterial cells, such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example, using T7 promoter regulatory sequences and T7 polymerase.

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, a nucleic acid molecule of the invention can be expressed in bacterial cells (*e.g.*, *E. coli*), insect cells, yeast, or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells, human 293T cells, HeLa cells, NIH 3T3 cells, and mouse erythroleukemia (MEL) cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing a foreign nucleic acid molecule (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al. (supra)*, and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select

these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those that confer resistance to drugs, such as G418, hygromycin, or methotrexate. Nucleic acid molecules encoding a selectable marker can be introduced into a host cell on the same vector as the nucleic acid molecule of the invention or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid molecule can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a polypeptide of the invention. Accordingly, the invention further provides methods for producing a polypeptide using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding a polypeptide of the invention has been introduced) in a suitable medium such that the polypeptide is produced. In another embodiment, the method further comprises isolating the polypeptide from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule of the invention has been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous nucleotide sequences have been introduced into the genome or homologous recombinant animals in which endogenous nucleotide sequences have been altered. Such animals are useful for studying the function and/or activity of the nucleotide sequence and polypeptide encoded by the sequence and for identifying and/or evaluating modulators of their activity.

As used herein, a "transgenic animal" is a non-human animal, preferably, a mammal, more preferably, a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, and amphibians. A

transgene is exogenous DNA that is integrated into the genome of a cell from which a transgenic animal develops and that remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably, a mammal, more preferably, a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191, and in Hogan, Manipulating the Mouse Embryo (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986)). Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, Current Opinion in Bio/Technology, 2:823-829 (1991) and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169. Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.*, Nature, 385:810-813 (1997) and PCT Publication Nos. WO 97/07668 and WO 97/07669.

ANTIBODIES OF THE INVENTION

Polyclonal and/or monoclonal antibodies that selectively bind one form of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide but not another form of the polypeptide are also provided. Antibodies are also provided that bind a portion of either the variant or reference HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide that contains the polymorphic site or sites.

In another aspect, the invention provides antibodies to each of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), and HDRP(ΔNLS) polypeptides and polypeptide fragments of the invention, *e.g.*, having an amino acid sequence encoded

by SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or a portion thereof, or having an amino acid sequence encoded by a nucleic acid molecule comprising all or a portion of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or another variant, or portion thereof).

The term "purified antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that selectively binds an antigen. A molecule that selectively binds to a polypeptide of the invention is a molecule that binds to that polypeptide or a fragment thereof, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample that naturally contains the polypeptide. Preferably the antibody is at least 60%, by weight, free from proteins and naturally occurring organic molecules with which it naturally associated. More preferably, the antibody preparation is at least 75% or 90%, and most preferably, 99%, by weight, antibody. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')2 fragments that can be generated by treating the antibody with an enzyme such as pepsin.

The invention provides polyclonal and monoclonal antibodies that selectively bind to an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide of the invention. The term "monoclonal antibody" or "monoclonal antibody composition," as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of a polypeptide of the invention. A monoclonal antibody composition thus typically displays a single binding affinity for a particular polypeptide of the invention with which it immunoreacts.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a desired immunogen, *e.g.*, an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide of the invention or fragment thereof. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules directed against the polypeptide can be isolated from the mammal (*e.g.*, from the

blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction.

At an appropriate time after immunization, *e.g.*, when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, Nature, 256:495-497 (1975), the human B cell hybridoma technique (Kozbor *et al.*, Immunol. Today, 4:72 (1983)), the EBV-hybridoma technique (Cole *et al.*, Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., pp. 77-96 (1985)) or trioma techniques. The technology for producing hybridomas is well known (see generally Current Protocols in Immunology, Coligan *et al.*, (eds.) John Wiley & Sons, Inc., New York, NY (1994)). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds a polypeptide of the invention.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal antibody to a polypeptide of the invention (see, *e.g.*, Current Protocols in Immunology, *supra*; Galfre *et al.*, (1977) Nature, 266:55052; R.H. Kenneth, in Monoclonal Antibodies: A New Dimension In Biological Analyses, Plenum Publishing Corp., New York, New York (1980); and Lerner, Yale J. Biol. Med., 54:387-402 (1981)). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods that also would be useful.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide to thereby isolate immunoglobulin library members that bind the polypeptide. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurfZAP™ Phage

Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.*, Bio/Technology, 9:1370-1372 (1991); Hay *et al.*, Hum. Antibod. Hybridomas, 3:81-85 (1992); Huse *et al.*, Science, 246:1275-1281 (1989); and Griffiths *et al.*, EMBO J., 12:725-734 (1993).

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art.

In general, antibodies of the invention (*e.g.*, a monoclonal antibody) can be used to isolate an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide of the invention by standard techniques, such as affinity chromatography or immunoprecipitation. A polypeptide-specific antibody can facilitate the purification of natural polypeptide from cells and of recombinantly produced polypeptide expressed in host cells. Moreover, an antibody specific for an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide of the invention can be used to detect the polypeptide (*e.g.*, in a cellular lysate, cell supernatant, or tissue sample) in order to evaluate the abundance and pattern of expression of the polypeptide.

The antibodies of the present invention can also be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, and acetylcholinesterase; examples of suitable

prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride and phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S, and ^{3}H.

DIAGNOSTIC AND SCREENING ASSAYS OF THE INVENTION

The present invention also pertains to diagnostic assays for assessing *HDAC 9 HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene expression, or for assessing activity of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptides of the invention. In one embodiment, the assays are used in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, or is at risk for (has a predisposition for or a susceptibility to) developing a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The invention also provides for prognostic (or predictive) assays for determining whether an individual is susceptible to developing a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. For example, mutations in the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of symptoms associated with a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Another aspect of the invention pertains to assays for monitoring the influence of agents, or candidate compounds (*e.g.*, drugs or other agents) on the nucleic acid molecule expression or biological activity of polypeptides of the invention, as well as to assays for identifying candidate compounds that bind to an HDAC9, HDAC9a polypeptide, an HDAC9(ΔNLS) polypeptide, an HDAC9a(ΔNLS) polypeptide, or an HDRP(ΔNLS) polypeptide. These and other assays and agents are described in further detail in the following sections.

DIAGNOSTIC ASSAYS

HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or *HDRP(ΔNLS)* nucleic acid molecules, probes, primers, polypeptides, and antibodies to an HDAC9, an HDAC9a protein, an HDAC9(ΔNLS) protein, an HDAC9a(ΔNLS) protein, or an HDRP(ΔNLS) protein can be used in methods of diagnosis of a susceptibility to, or likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, as well as in kits useful for diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In one embodiment of the invention, diagnosis of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease is made by detecting a polymorphism in *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. The polymorphism can be a mutation in *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, such as the insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift mutation; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of the gene; duplication of all or a part of the gene; transposition of all or a part of the gene; or rearrangement of all or a part of the gene, or a change in the expression pattern of the various HDAC9 isoforms. More than one such mutation may be present in a single nucleic acid molecule.

Such sequence changes cause a mutation in the polypeptide encoded by *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. For example, if the mutation is a frame shift mutation, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a premature stop codon, causing generation of a truncated polypeptide. Alternatively, a polymorphism associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease can be a synonymous

mutation in one or more nucleotides (*i.e.*, a mutation that does not result in a change in the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide). Such a polymorphism may alter sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the nucleic acid molecule. *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* that has any of the mutations described above is referred to herein as a "mutant nucleic acid molecule."

In a first method of diagnosing a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, hybridization methods, such as Southern analysis, Northern analysis, or *in situ* hybridizations, can be used (see Ausubel, *et al.*, *supra*). For example, a biological sample from a test subject (a "test sample") of genomic DNA, RNA, or cDNA, is obtained from an individual suspected of having, being susceptible to or predisposed for, or carrying a defect for, a cell proliferation disease, an apoptotic disease, or a cell differentiation disease (the "test individual"). The individual can be an adult, child, or fetus. The test sample can be from any source that contains genomic DNA, such as a blood sample, sample of amniotic fluid, sample of cerebrospinal fluid, or tissue sample from skin, muscle, buccal or conjunctival mucosa, placenta, gastrointestinal tract, or other organs. A test sample of DNA from fetal cells or tissue can be obtained by appropriate methods, such as by amniocentesis or chorionic villus sampling. The DNA, RNA, or cDNA sample is then examined to determine whether a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is present, and/or to determine which variant(s) encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is present. The presence of the polymorphism or variant(s) can be indicated by hybridization of the gene in the genomic DNA, RNA, or cDNA to a nucleic acid probe. A "nucleic acid probe," as used herein, can be a DNA probe or an RNA probe; the nucleic acid probe can contain at least one polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or contains a nucleic acid encoding a particular variant of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS). The probe can be any of the nucleic acid

molecules described above (*e.g.*, the entire nucleic acid molecule, a fragment, a vector comprising the gene, a probe, or primer, etc.).

To diagnose a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, a hybridization sample is formed by contacting the test sample containing *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, with at least one nucleic acid probe. A preferred probe for detecting mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA or genomic DNA sequences described herein. The nucleic acid probe can be, for example, a full-length nucleic acid molecule, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250, or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to appropriate mRNA or genomic DNA. For example, the nucleic acid probe can be all or a portion of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or the complement of SEQ ID NO: 1 or SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9; or can be a nucleic acid molecule encoding all or a portion of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. Other suitable probes for use in the diagnostic assays of the invention are described above (see. *e.g.*, probes and primers discussed under the heading, "Nucleic Acids of the Invention").

The hybridization sample is maintained under conditions that are sufficient to allow specific hybridization of the nucleic acid probe to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. "Specific hybridization," as used herein, indicates exact hybridization (*e.g.*, with no mismatches). Specific hybridization can be performed under high stringency conditions or moderate stringency conditions, for example, as described above. In a particularly preferred embodiment, the hybridization conditions for specific hybridization are high stringency.

Specific hybridization, if present, is then detected using standard methods. If specific hybridization occurs between the nucleic acid probe and *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in the test sample, then *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* has the

polymorphism, or is the variant, that is present in the nucleic acid probe. More than one nucleic acid probe can also be used concurrently in this method. Specific hybridization of any one of the nucleic acid probes is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or of the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is therefore diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In Northern analysis (see Current Protocols in Molecular Biology, Ausubel, *et al.*, *supra*), the hybridization methods described above are used to identify the presence of a polymorphism or of a particular variant, associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. For Northern analysis, a test sample of RNA is obtained from the individual by appropriate means. Specific hybridization of a nucleic acid probe, as described above, to RNA from the individual is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or of the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is therefore diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

For representative examples of use of nucleic acid probes, see, for example, U.S. Patent Nos. 5,288,611 and 4,851,330.

Alternatively, a peptide nucleic acid (PNA) probe can be used instead of a nucleic acid probe in the hybridization methods described above. PNA is a DNA mimic having a peptide-like, inorganic backbone, such as N-(2-aminoethyl)glycine units, with an organic base (A, G, C, T, or U) attached to the glycine nitrogen via a methylene carbonyl linker (see, for example, Nielsen *et al.*, Bioconjugate Chemistry, 5 (1994), American Chemical Society, p. 1 (1994)). The PNA probe can be designed to specifically hybridize to a gene having a polymorphism associated with a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. Hybridization of the PNA probe to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is diagnostic for a decreased

susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In another method of the invention, mutation analysis by restriction digestion can be used to detect a mutant nucleic acid molecule, or nucleic acid molecules containing a polymorphism(s), if the mutation or polymorphism in the gene results in the creation or elimination of a restriction site. A test sample containing genomic DNA is obtained from the individual. Polymerase chain reaction (PCR) can be used to amplify *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (and, if necessary, the flanking sequences) in the test sample of genomic DNA from the test individual. RFLP analysis is conducted as described (see Current Protocols in Molecular Biology, *supra*). The digestion pattern of the relevant DNA fragment indicates the presence or absence of the mutation or polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and therefore indicates the presence or absence of this decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Sequence analysis can also be used to detect specific polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. A test sample of DNA or RNA is obtained from the test individual. PCR or other appropriate methods can be used to amplify the nucleic acid molecule, and/or its flanking sequences, if desired. The sequence of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or HDRP(ΔNLS), or a fragment of the any of those nucleic acid molecules, or an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* cDNA, or a fragment of any of those cDNAs, or an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA, or a fragment of any of those mRNAs, is determined, using standard methods. The sequence of the above gene, gene fragment, cDNA, cDNA fragment, mRNA, or mRNA fragment is compared with the known nucleic acid sequence of the nucleic acid molecule, cDNA (*e.g.*, SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a nucleic acid sequence encoding the protein of SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO: 10, or a fragment thereof) or mRNA, as appropriate. The presence of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* indicates that the

individual has a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Allele-specific oligonucleotides can also be used to detect the presence of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, through the use of dot-blot hybridization of amplified oligonucleotides with allele-specific oligonucleotide (ASO) probes (see, for example, Saiki *et al.*, Nature (London) 324:163-166 (1986)). An "allele-specific oligonucleotide" (also referred to herein as an "allele-specific oligonucleotide probe") is an oligonucleotide of approximately 10-50 base pairs, preferably approximately 15-30 base pairs, that specifically hybridizes to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and that contains a polymorphism associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. An allele-specific oligonucleotide probe that is specific for particular polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be prepared, using standard methods (see Current Protocols in Molecular Biology, *supra*).

To identify polymorphisms in the gene that are associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease a test sample of DNA is obtained from the individual. PCR can be used to amplify all or a fragment of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and its flanking sequences. The DNA containing the amplified *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (or a fragment of any of those genes) is dot-blotted, using standard methods (see Current Protocols in Molecular Biology, *supra*), and the blot is contacted with the oligonucleotide probe. The presence of specific hybridization of the probe to the amplified *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is then detected. Specific hybridization of an allele-specific oligonucleotide probe to DNA from the individual is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is therefore indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In another embodiment, arrays of oligonucleotide probes that are complementary to target nucleic acid sequence segments from an individual, can be used to identify polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. For example, in one embodiment, an oligonucleotide array can be used. Oligonucleotide arrays typically comprise a plurality of different oligonucleotide probes that are coupled to a surface of a substrate in different known locations. These oligonucleotide arrays, also described as "GENECHIPS™," have been generally described in the art, for example, U.S. Patent No. 5,143,854 and PCT patent publication Nos. WO 90/15070 and 92/10092. These arrays can generally be produced using mechanical synthesis methods or light directed synthesis methods that incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis methods. See Fodor *et al.*, Science, 251:767-777 (1991), Pirrung *et al.*, U.S. Patent No. 5,143,854; PCT Publication No. WO 90/15070; Fodor *et al.*, PCT Publication No. WO 92/10092, and U.S. Patent No. 5,424,186, the entire teachings of each of which are incorporated by reference herein. Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, *e.g.*, U.S. Patent No. 5,384,261, the entire teachings of which are incorporated by reference herein.

Once an oligonucleotide array is prepared, a nucleic acid of interest is hybridized to the array and scanned for polymorphisms. Hybridization and scanning are generally carried out by methods described herein and also in, *e.g.*, Published PCT Application Nos. WO 92/10092 and WO 95/11995, and U.S. Patent No. 5,424,186, the entire teachings of which are incorporated by reference herein. In brief, a target nucleic acid sequence that includes one or more previously identified polymorphic markers is amplified by well known amplification techniques, *e.g.*, PCR. Typically, this involves the use of primer sequences that are complementary to the two strands of the target sequence both upstream and downstream from the polymorphism. Asymmetric PCR techniques may also be used. Amplified target, generally incorporating a label, is then hybridized with the array under appropriate conditions. Upon completion of hybridization and washing of the array, the array is scanned to determine the position on the array to which the target sequence

hybridizes. The hybridization data obtained from the scan is typically in the form of fluorescence intensities as a function of location on the array.

Although primarily described in terms of a single detection block, *e.g.*, for detection of a single polymorphism, arrays can include multiple detection blocks, and thus be capable of analyzing multiple, specific polymorphisms. In alternate arrangements, it will generally be understood that detection blocks may be grouped within a single array or in multiple, separate arrays so that varying, optimal conditions may be used during the hybridization of the target to the array. For example, it may often be desirable to provide for the detection of those polymorphisms that fall within G-C rich stretches of a genomic sequence, separately from those falling in A-T rich segments. This allows for the separate optimization of hybridization conditions for each situation.

Additional descriptions of the use of oligonucleotide arrays for detection of polymorphisms can be found, for example, in U.S. Patent Nos. 5,858,659 and 5,837,832, the entire teachings of which are incorporated by reference herein.

Other methods of nucleic acid analysis can be used to detect polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. Representative methods include direct manual sequencing (Church and Gilbert Proc. Natl. Acad. Sci. USA 81: 1991-1995, (1988); Sanger *et al.*, Proc. Natl. Acad. Sci. 74: 5463-5467 (1977); Beavis *et al.*, U.S. Patent No. 5,288,644); automated fluorescent sequencing; single-stranded conformation polymorphism assays (SSCP); clamped denaturing gel electrophoresis (CDGE); denaturing gradient gel electrophoresis (DGGE) (Sheffield *et al.*, Proc. Natl. Acad. Sci. USA 86: 232-236 (1991)), mobility shift analysis (Orita *et al.*, Proc. Natl. Acad. Sci. USA 86: 2766-2770 (1989)), restriction enzyme analysis (Flavell *et al.*, Cell 15: 25 (1978); Geever, *et al.*, Proc. Natl. Acad. Sci. USA 78: 5081 (1981)); heteroduplex analysis; chemical mismatch cleavage (CMC) (Cotton *et al.*, Proc. Natl. Acad. Sci. USA 85: 4397-4401 (1985)); RNase protection assays (Myers *et al.*, Science 230: 1242 (1985)); use of polypeptides that recognize nucleotide mismatches, such as *E. coli* mutS protein; and allele-specific PCR.

In another embodiment of the invention, diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease can also be made by examining the level of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid, for example, using in situ hybridization techniques known to one skilled in the art, or by examining the level of expression, activity, and/or composition of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, by a variety of methods, including enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, immunohistochemistry, and immunofluorescence. A test sample from an individual is assessed for the presence of an alteration in the level of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid or in the expression and/or an alteration in composition of the polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or for the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. An alteration in expression of a polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be, for example, an alteration in the quantitative polypeptide expression (*i.e.*, the amount of polypeptide produced); an alteration in the composition of a polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or an alteration in the qualitative polypeptide expression (*e.g.*, expression of a mutant HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide or variant thereof). In a preferred embodiment, diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease is made by detecting a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or a particular pattern of variants. Preferably, increased levels of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or increased expression or activity of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, relative to a control sample, for example, a sample known not to be associated with a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, indicates an increased susceptibility or likelihood that the individual has a cell proliferation disease, an apoptotic disease, or a cell

differentiation disease. Alternatively, decreased levels of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or decreased expression or activity of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, relative to a control sample, for example, a sample known not to be associated with a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, indicates a decreased susceptibility or likelihood that the individual has a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Both quantitative and qualitative alterations can also be present. An "alteration" or "modulation" in the polypeptide expression, activity, or composition, as used herein, refers to an alteration in expression or composition in a test sample, as compared with the expression or composition of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide in a control sample. A control sample is a sample that corresponds to the test sample (*e.g.*, is from the same type of cells), and is from an individual who is not affected by a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. An alteration in the expression or composition of the polypeptide in the test sample, as compared with the control sample, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. Similarly, the presence of one or more different variants in the test sample, or the presence of significantly different amounts of different variants in the test sample, as compared with the control sample, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

It is understood that alterations or modulations in polypeptide expression or function can occur in varying degrees. For example, an alteration or modulation in expression can be an increase, for example, by at least 1.5-fold to 2-fold, at least 3-fold, or, at least 5-fold, relative to the control. Alternatively, the alteration or modulation in polypeptide expression can be a decrease, for example, by at least 10%, at least 40%, 50%, or 75%, or by at least 90%, relative to the control.

Various means of examining expression or composition of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide can be used, including spectroscopy, colorimetry, electrophoresis, isoelectric focusing, and

immunoassays (*e.g.*, David *et al.*, U.S. Patent No. 4,376,110) such as immunoblotting (see also Ausubel *et al.*, *supra*; particularly chapter 10). For example, in one embodiment, an antibody capable of binding to the polypeptide (*e.g.*, as described above), preferably an antibody with a detectable label, can be used. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')2) can be used. The term "labeled," with regard to the antibody, is intended to encompass direct labeling of the antibody by coupling (*i.e.*, physically linking) a detectable substance to the antibody, as well as indirect labeling of the antibody by reacting it with another reagent that is directly labeled. An example of indirect labeling is detection of a primary antibody using a fluorescently labeled secondary antibody.

Western blotting analysis, using an antibody as described above that specifically binds to a mutant HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, or an antibody that specifically binds to a non-mutant HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, or an antibody that specifically binds to a particular variant encoded by *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, can be used to identify the presence in a test sample of a particular variant of a polypeptide encoded by a polymorphic or mutant *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or the absence in a test sample of a particular variant or of a polypeptide encoded by a non-polymorphic or non-mutant gene. The presence of a polypeptide encoded by a polymorphic or mutant gene, or the absence of a polypeptide encoded by a non-polymorphic or non-mutant gene, is diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, as is the presence (or absence) of particular variants encoded by the *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule.

In one embodiment of this method, the level or amount of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide in a test sample is compared with the level or amount of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide in a control sample. A level or amount of the polypeptide in the test sample that is higher or

lower than the level or amount of the polypeptide in the control sample, such that the difference is statistically significant, is indicative of an alteration in the expression of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, and is diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Alternatively, the composition of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide in a test sample is compared with the composition of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide in a control sample. A difference in the composition of the polypeptide in the test sample, as compared with the composition of the polypeptide in the control sample (*e.g.*, the presence of different variants), is diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In another embodiment, both the level or amount and the composition of the polypeptide can be assessed in the test sample and in the control sample. A difference in the amount or level of the polypeptide in the test sample, compared to the control sample; a difference in composition in the test sample, compared to the control sample; or both a difference in the amount or level, and a difference in the composition, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Kits (*e.g.*, reagent kits) useful in the methods of diagnosis comprise components useful in any of the methods described herein, including, for example, hybridization probes or primers as described herein (*e.g.*, labeled probes or primers), reagents for detection of labeled molecules, restriction enzymes (*e.g.*, for RFLP analysis), allele-specific oligonucleotides, antibodies that bind to a mutant or to non-mutant (native) HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, means for amplification of nucleic acids comprising *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or means for analyzing the nucleic acid sequence of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or for analyzing the amino acid sequence of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, etc.

SCREENING ASSAYS AND AGENTS IDENTIFIED THEREBY

The invention provides methods (also referred to herein as "screening assays") for identifying the presence of a nucleotide that hybridizes to a nucleic acid of the invention, as well as for identifying the presence of a polypeptide encoded by a nucleic acid of the invention. In one embodiment, the presence (or absence) of a nucleic acid molecule of interest (*e.g.*, a nucleic acid that has significant homology with a nucleic acid of *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*) in a sample can be assessed by contacting the sample with a nucleic acid comprising a nucleic acid of the invention (*e.g.*, a nucleic acid having the sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or the complement thereof, or a nucleic acid encoding an amino acid having the sequence of SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or a fragment or variant of such nucleic acids), under stringent conditions as described above, and then assessing the sample for the presence (or absence) of hybridization. In a preferred embodiment, high stringency conditions are conditions appropriate for selective hybridization. In another embodiment, a sample containing the nucleic acid molecule of interest is contacted with a nucleic acid containing a contiguous nucleotide sequence (*e.g.*, a primer or a probe as described above) that is at least partially complementary to a part of the nucleic acid molecule of interest (*e.g.*, an *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid), and the contacted sample is assessed for the presence or absence of hybridization. In a preferred embodiment, the nucleic acid containing a contiguous nucleotide sequence is completely complementary to a part of the nucleic acid molecule of *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*.

In any of the above embodiments, all or a portion of the nucleic acid of interest can be subjected to amplification prior to performing the hybridization.

In another embodiment, the presence (or absence) of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, such as a polypeptide of the invention or a fragment or variant thereof, in a sample can be assessed by contacting the sample with an antibody that specifically binds to the

polypeptide of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) (*e.g.*, an antibody such as those described above), and then assessing the sample for the presence (or absence) of binding of the antibody to the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide.

In another embodiment, the invention provides methods for identifying agents or compounds (*e.g.*, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) that alter or modulate (*e.g.*, increase or decrease) the activity of the polypeptides described herein, or that otherwise interact with the polypeptides herein. For example, such compounds can be compounds or agents that bind to polypeptides described herein (*e.g.*, HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrates or agents); that have a stimulatory or inhibitory effect on, for example, activity of polypeptides of the invention; or that change (*e.g.*, enhance or inhibit) the ability of the polypeptides of the invention to interact with HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) binding agents; or that alter post-translational processing of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide (*e.g.*, agents that alter proteolytic processing to direct the polypeptide from where it is normally synthesized to another location in the cell, such as the cell surface; or agents that alter proteolytic processing such that more polypeptide is released from the cell, etc.). In one example, the binding agent is a cell proliferation disease binding agent, an apoptotic disease binding agent, or a cell differentiation disease binding agent. As used herein, by a "cell proliferation disease binding agent," an "apoptotic disease binding agent," or a "cell differentiation disease binding agent" is meant an agent as described herein that binds to a polypeptide of the present invention and modulates a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The modulation can be an increase or a decrease in the severity or progression of the disease. In addition, a cell proliferation disease binding agent, an apoptotic disease binding agent, or a cell differentiation disease binding agent includes an agent that binds to a polypeptide that is upstream (earlier) or downstream (later) of the cell signaling events mediated by a polypeptide of the

present invention, and thereby modulates the overall activity of the signaling pathway; in turn, the disease state is modulated.

The candidate compound can cause an increase in the activity of the polypeptide. For example, the activity of the polypeptide can be increased by at least 1.5-fold to 2-fold, at least 3-fold, or, at least 5-fold, relative to the control. Alternatively, the polypeptide activity can be a decrease, for example, by at least 10%, at least 20%, 40%, 50%, or 75%, or by at least 90%, relative to the control.

In one embodiment, the invention provides assays for screening candidate compounds or test agents to identify compounds that bind to or modulate the activity of polypeptides described herein (or biologically active portion(s) thereof), as well as agents identifiable by the assays. As used herein, a "candidate compound" or "test agent" is a chemical molecule, be it naturally-occurring or artificially-derived, and includes, for example, peptides, proteins, synthesized molecules, for example, synthetic organic molecules, naturally-occurring molecule, for example, naturally occurring organic molecules, nucleic acid molecules, and components thereof.

In general, candidate compounds for uses in the present invention may be identified from large libraries of natural products or synthetic (or semi-synthetic) extracts or chemical libraries according to methods known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the screening procedure(s) of the invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using the exemplary methods described herein. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or animal-based extracts, fermentation broths, and synthetic compounds, as well as modification of existing compounds. Numerous methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid-based compounds. Synthetic compound libraries are commercially available, e.g., from Brandon Associates (Merrimack, NH) and Aldrich Chemical (Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova

(Slough, UK), Harbor Branch Oceangraphics Institute (Ft. Pierce, FL), and PharmaMar, U.S.A. (Cambridge, MA). In addition, natural and synthetically produced libraries are generated, if desired, according to methods known in the art, e.g., by standard extraction and fractionation methods. For example, candidate compounds can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of compounds (Lam, Anticancer Drug Des., 12: 145 (1997)). Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (e.g., taxonomic dereplication, biological dereplication, and chemical dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known for their activities should be employed whenever possible.

When a crude extract is found to modulate (i.e., stimulate or inhibit) the expression and/or activity of the nucleic acids and or polypeptides of the present invention, further fractionation of the positive lead extract is necessary to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and identification of a chemical entity within the crude extract having an activity that stimulates or inhibits nucleic acid expression, polypeptide expression, or polypeptide biological activity. The same assays described herein for the detection of activities in mixtures of compounds can be used to purify the active component and to test derivatives thereof. Methods of fractionation and purification of such heterogenous extracts are known in the art. If desired, compounds shown to be useful agents for treatment are chemically modified according to methods known in the art. Compounds identified as being of therapeutic value may be subsequently analyzed

using animal models for diseases in which it is desirable to alter the activity or expression of the nucleic acids or polypeptides of the present invention.

In one embodiment, to identify candidate compounds that alter the biological activity, for example, the enzymatic activity or transcriptional repression activity of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, a cell, tissue, cell lysate, tissue lysate, or solution containing or expressing an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SE ID NO: 8, SEQ ID NO: 10, or another variant encoded by *HDAC9, HDAC9a, HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*), or a fragment or derivative thereof (as described above), can be contacted with a candidate compound to be tested under conditions suitable for enzymatic reaction or transcriptional repression reaction, as described herein.

Alternatively, the polypeptide can be contacted directly with the candidate compound to be tested. The level (amount) of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) biological activity is assessed (*e.g.*, the level (amount) of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) biological activity is measured, either directly or indirectly), and is compared with the level of biological activity in a control (*i.e.*, the level of activity of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide or active fragment or derivative thereof in the absence of the candidate compound to be tested, or in the presence of the candidate compound vehicle only). If the level of the biological activity in the presence of the candidate compound differs, by an amount that is statistically significant, from the level of the biological activity in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a compound that alters the biological activity of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide. For example, an increase in the level of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) enzymatic or transcriptional repression activity relative to a control, indicates that the candidate compound is a compound that enhances (is an agonist of) HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) activity. Similarly,

a decrease in the enzymatic level or transcriptional repression level of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) activity relative to a control, indicates that the candidate compound is a compound that inhibits (is an antagonist of) HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) activity. In another embodiment, the level of biological activity of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide or derivative or fragment thereof in the presence of the candidate compound to be tested, is compared with a control level that has previously been established. A level of the biological activity in the presence of the candidate compound that differs from the control level by an amount that is statistically significant indicates that the compound alters HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) biological activity.

The present invention also relates to an assay for identifying compounds that alter the expression of an *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS)* nucleic acid molecule (*e.g.*, antisense nucleic acids, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) that alter (*e.g.*, increase or decrease) expression (*e.g.*, transcription or translation) of the nucleic acid molecule or that otherwise interact with the nucleic acids described herein, as well as compounds identifiable by the assays. For example, a solution containing a nucleic acid encoding an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide can be contacted with a candidate compound to be tested. The solution can comprise, for example, cells containing the nucleic acid or cell lysate containing the nucleic acid; alternatively, the solution can be another solution that comprises elements necessary for transcription/translation of the nucleic acid. Cells not suspended in solution can also be employed, if desired. The level and/or pattern of *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS)* expression (*e.g.*, the level and/or pattern of mRNA or of protein expressed, such as the level and/or pattern of different variants) is assessed, and is compared with the level and/or pattern of expression in a control (*i.e.*, the level and/or pattern of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression in the absence of the candidate compound, or in the presence of the candidate

compound vehicle only). If the level and/or pattern in the presence of the candidate compound differs, by an amount or in a manner that is statistically significant, from the level and/or pattern in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a compound that alters the expression of *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. Enhancement of *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression indicates that the candidate compound is an agonist of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) activity. Similarly, inhibition of *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression indicates that the candidate compound is an antagonist of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) activity. In another embodiment, the level and/or pattern of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide(s) (*e.g.*, different variants) in the presence of the candidate compound to be tested, is compared with a control level and/or pattern that has previously been established. A level and/or pattern in the presence of the candidate compound that differs from the control level and/or pattern by an amount or in a manner that is statistically significant indicates that the candidate compound alters *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression.

In another embodiment of the invention, compounds that alter the expression of an *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule or that otherwise interact with the nucleic acids described herein, can be identified using a cell, cell lysate, or solution containing a nucleic acid encoding the promoter region of the *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene operably linked to a reporter gene. After contact with a candidate compound to be tested, the level of expression of the reporter gene (*e.g.*, the level of mRNA or of protein expressed) is assessed, and is compared with the level of expression in a control (*i.e.*, the level of the expression of the reporter gene in the absence of the candidate compound, or in the presence of the candidate compound vehicle only). If the level in the presence of the candidate compound differs, by an amount or in a manner that is statistically significant, from

the level in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a compound that alters the expression of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, as indicated by its ability to alter expression of a gene that is operably linked to the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene promoter. Enhancement of the expression of the reporter indicates that the compound is an agonist of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) activity. Similarly, inhibition of the expression of the reporter indicates that the compound is an antagonist of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) activity. In another embodiment, the level of expression of the reporter in the presence of the candidate compound to be tested, is compared with a control level that has previously been established. A level in the presence of the candidate compound that differs from the control level by an amount or in a manner that is statistically significant indicates that the candidate compound alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression.

Compounds that alter the amounts of different variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (*e.g.*, a compound that enhances activity of a first variant, and that inhibits activity of a second variant), as well as compounds that are agonists of activity of a first variant and antagonists of activity of a second variant, can easily be identified using these methods described above.

In other embodiments of the invention, assays can be used to assess the impact of a candidate compound on the activity of a polypeptide in relation to an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrate, for example, an inhibitor of histone deacetylase activity. These inhibitors fall into four general classes: 1) short-chain fatty acids (*e.g.*, 4-phenylbutyrate and valproic acid); 2) hydroxamic acids (*e.g.*, SAHA, Pyroxamide, trichostatin A (TSA), oxamflatin and CHAPs, such as, CHAP1 and CHAP 31); 3) cyclic tetrapeptides (Trapoxin A, Apicidin and Depsipeptide (FK-228, also known as FR9011228); 4) benzamides (*e.g.*, MS-275); and other compounds such as Scriptaid. Examples of such assays and compounds can be found in U.S. Patent Nos. 5,369,108, issued on

November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, as well as, Yoshida *et al.*, *supra*; Saito *et al.*, *supra*; Furamai *et al.*, *supra*; Komatsu *et al.*, *supra*; Su *et al.*, *supra*; Lee *et al.*, *supra* and Suzuki *et al. supra*, the entire content of all of which are hereby incorporated by reference.

In one example, a cell or tissue that expresses or contains a compound that interacts with HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) (herein referred to as an "HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrate," which can be a polypeptide or other molecule that interacts with HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS)) is contacted with HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) in the presence of a candidate compound, and the ability of the candidate compound to alter the interaction between HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) and the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP (ΔNLS) substrate is determined, for example, by assaying activity of the polypeptide. Alternatively, a cell lysate or a solution containing the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrate, can be used. A compound that binds to HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) or the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrate can alter the interaction by interfering with, or enhancing the ability of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) to bind to, associate with, or otherwise interact with the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrate.

Determining the ability of the candidate compound to bind to HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) or an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrate can be accomplished, for example, by coupling the candidate compound with a radioisotope or enzymatic label such that binding of the candidate compound to the polypeptide can be determined by detecting the labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of

radioemmission or by scintillation counting. Alternatively, candidate compound can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

It is also within the scope of this invention to determine the ability of a candidate compound to interact with the polypeptide without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a candidate compound with HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) or an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrate without the labeling of either the candidate compound, HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS), or the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrate (McConnell *et al.*, (1992) Science, 257: 1906-1912). As used herein, a "microphysiometer" (*e.g.*, CYTOSENSOR™) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between ligand and polypeptide.

In another embodiment of the invention, assays can be used to identify polypeptides that interact with one or more HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptides, as described herein. For example, a yeast two-hybrid system such as that described by Fields and Song (Fields and Song, Nature 340: 245-246 (1989)) can be used to identify polypeptides that interact with one or more HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptides. In such a yeast two-hybrid system, vectors are constructed based on the flexibility of a transcription factor that has two functional domains (a DNA binding domain and a transcription activation domain). If the two domains are separated but fused to two different proteins that interact with one another, transcriptional activation can be achieved, and transcription of specific markers (*e.g.*, nutritional markers such as His and Ade, or color markers such as lacZ) can be used to identify the presence of interaction and transcriptional activation. For example, in the methods of the invention, a first vector is used that includes a nucleic acid encoding a DNA binding domain and an HDAC9, HDAC9a,

HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, variant, or fragment or derivative thereof, and a second vector is used that includes a nucleic acid encoding a transcription activation domain and a nucleic acid encoding a polypeptide that potentially may interact with the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, variant, or fragment or derivative thereof (*e.g.*, an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide substrate or receptor). Incubation of yeast containing the first vector and the second vector under appropriate conditions (*e.g.*, mating conditions such as used in the MATCHMAKER™ system from Clontech) allows identification of colonies that express the markers of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS). These colonies can be examined to identify the polypeptide(s) that interact with the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide or fragment or derivative thereof. Such polypeptides may be useful as compounds that alter the activity or expression of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, as described above.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, or an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrate, or other components of the assay on a solid support, in order to facilitate separation of complexed from uncomplexed forms of one or both of the polypeptides, as well as to accommodate automation of the assay. Binding of a candidate compound to the polypeptide, or interaction of the polypeptide with a substrate in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein (*e.g.*, a glutathione-S-transferase fusion protein) can be provided that adds a domain that allows HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) or an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrate to be bound to a matrix or other solid support.

In another embodiment, modulators of expression of nucleic acid molecules of the invention are identified in a method wherein a cell, cell lysate, tissue, tissue lysate, or solution containing a nucleic acid encoding HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) is contacted with a candidate compound and the expression of appropriate mRNA or polypeptide (*e.g.*, variant(s)) in the cell, cell lysate, tissue, or tissue lysate, or solution, is determined. The level of expression of appropriate mRNA or polypeptide(s) in the presence of the candidate compound is compared to the level of expression of mRNA or polypeptide(s) in the absence of the candidate compound, or in the presence of the candidate compound vehicle only. The candidate compound can then be identified as a modulator of expression based on this comparison. For example, when expression of mRNA or polypeptide is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator or enhancer of the mRNA or polypeptide expression. Alternatively, when expression of the mRNA or polypeptide is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of the mRNA or polypeptide expression. The level of mRNA or polypeptide expression in the cells can be determined by methods described herein for detecting mRNA or polypeptide.

This invention further pertains to novel compounds identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use a compound identified as described herein in an appropriate animal model. For example, a compound identified as described herein (*e.g.*, a candidate compound that is a modulating compound such as an antisense nucleic acid molecule, a specific antibody, or a polypeptide substrate) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such a compound. Alternatively, a compound identified as described herein can be used in an animal model to determine the mechanism of action of such a compound. Furthermore, this invention pertains to uses of novel compounds identified by the above-described screening assays for treatments as described herein. In addition, a compound identified as described herein can be used to alter activity of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, or to

alter expression of *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, by contacting the polypeptide or the nucleic acid molecule (or contacting a cell comprising the polypeptide or the nucleic acid molecule) with the compound identified as described herein.

PHARMACEUTICAL COMPOSITIONS

The present invention also pertains to pharmaceutical compositions comprising nucleic acids described herein, particularly nucleotides encoding the polypeptides described herein; comprising polypeptides described herein (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO:10, and/or other variants encoded by *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*); and/or comprising a compound that alters (*e.g.*, increases or decreases) *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression or HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide activity as described herein. For instance, a polypeptide, protein, fragment, fusion protein or prodrug thereof, or a nucleotide or nucleic acid construct (vector) comprising a nucleotide of the present invention, a compound that alters HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide activity, a compound that alters *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid expression, or an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrate or binding partner, can be formulated with a physiologically acceptable carrier or excipient to prepare a pharmaceutical composition. The carrier and composition can be sterile. The formulation should suit the mode of administration.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (*e.g.*, NaCl), saline, buffered saline, alcohols, glycerol, ethanol, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, dextrose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, etc., as well as combinations thereof. The pharmaceutical preparations can, if desired, be mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic

pressure, buffers, coloring, flavoring and/or aromatic substances and the like that do not deleteriously react with the active compounds.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, polyvinyl pyrollidone, sodium saccharine, cellulose, magnesium carbonate, etc.

Methods of introduction of these compositions include, but are not limited to, intradermal, intramuscular, intraperitoneal, intraocular, intravenous, subcutaneous, topical, oral and intranasal. Other suitable methods of introduction can also include gene therapy (as described below), rechargeable or biodegradable devices, particle acceleration devises ("gene guns") and slow release polymeric devices. The pharmaceutical compositions of this invention can also be administered as part of a combinatorial therapy with other compounds.

The composition can be formulated in accordance with the routine procedures as a pharmaceutical composition adapted for administration to human beings. For example, compositions for intravenous administration typically are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active compound. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

For topical application, nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a

dynamic viscosity preferably greater than water, can be employed. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, enemas, lotions, sols, liniments, salves, aerosols, etc., that are, if desired, sterilized or mixed with auxiliary agents, *e.g.*, preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. The compound may be incorporated into a cosmetic formulation. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, *e.g.*, pressurized air.

Compounds described herein can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The compounds are administered in a therapeutically effective amount. The amount of compounds that will be therapeutically effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the symptoms of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, that notice

reflects approval by the agency of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug administration (*e.g.*, separately, sequentially or concurrently), or the like. The pack or kit may also include means for reminding the patient to take the therapy. The pack or kit can be a single unit dosage of the combination therapy or it can be a plurality of unit dosages. In particular, the compounds can be separated, mixed together in any combination, present in a single vial or tablet. Compounds assembled in a blister pack or other dispensing means is preferred. For the purpose of this invention, unit dosage is intended to mean a dosage that is dependent on the individual pharmacodynamics of each compound and administered in FDA approved dosages in standard time courses.

METHODS OF THERAPY

The present invention also pertains to methods of treatment (prophylactic, diagnostic, and/or therapeutic) for a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, using an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) therapeutic compound. An "HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) therapeutic compound" is a compound that alters (*e.g.*, enhances or inhibits) HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide activity and/or *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule expression, as described herein (*e.g.*, an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) agonist or antagonist). HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) therapeutic compounds can alter HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide activity or nucleic acid molecule expression by a variety of means, such as, for example, by providing additional HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide or by upregulating the transcription or translation of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule; by altering post-translational processing of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide; by altering

transcription of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* variants; or by interfering with HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide activity (*e.g.*, by binding to an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide), or by downregulating the transcription or translation of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule. Representative HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) therapeutic compounds include the following: nucleic acids or fragments or derivatives thereof described herein, particularly nucleotides encoding the polypeptides described herein and vectors comprising such nucleic acids (*e.g.*, a nucleic acid molecule, cDNA, and/or RNA, such as a nucleic acid encoding an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide or active fragment or derivative thereof, or an oligonucleotide; for example, SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or a nucleic acid encoding SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or fragments or derivatives thereof); polypeptides described herein (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8 SEQ ID NO: 10 and/or other variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or fragments or derivatives thereof); HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) substrates; peptidomimetics; fusion proteins or prodrugs thereof; antibodies (*e.g.*, an antibody to a mutant HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, or an antibody to a non-mutant HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, or an antibody to a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, as described above); ribozymes; other small molecules; and other compounds that alter (*e.g.*, enhance or inhibit) *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid expression or polypeptide activity, for example, those compounds identified in the screening methods described herein, or that regulate transcription of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* variants (*e.g.*,

compounds that affect which variants are expressed, or that affect the amount of each variant that is expressed. More than one HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) therapeutic compound can be used concurrently, if desired.

The HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) therapeutic compound that is a nucleic acid is used in the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The term, "treatment" as used herein, refers not only to ameliorating symptoms associated with the disease, but also preventing or delaying the onset of the disease, and also lessening the severity or frequency of symptoms of the disease. The therapy is designed to alter (*e.g.*, inhibit or enhance), replace or supplement activity of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide in an individual. For example, an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) therapeutic compound can be administered in order to upregulate or increase the expression or availability of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule or of specific variants of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS), or, conversely, to downregulate or decrease the expression or availability of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule or specific variants of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS). Upregulation or increasing expression or availability of a native *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule or of a particular variant could interfere with or compensate for the expression or activity of a defective gene or another variant; downregulation or decreasing expression or availability of a native *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule or of a particular variant could minimize the expression or activity of a defective gene or the particular variant and thereby minimize the impact of the defective gene or the particular variant.

The HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) therapeutic compound(s) are administered in a therapeutically effective amount (*i.e.*, an amount that is sufficient to treat the disease, such as by

ameliorating symptoms associated with the disease, preventing or delaying the onset of the disease, and/or also lessening the severity or frequency of symptoms of the disease). The amount that will be therapeutically effective in the treatment of a particular individual's disorder or condition will depend on the symptoms and severity of the disease, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

In one embodiment, a nucleic acid of the invention (*e.g.*, a nucleic acid encoding an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, such as SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or a nucleic acid that encodes an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide or a variant, derivative or fragment thereof, such as a nucleic acid encoding the protein of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10) can be used, either alone or in a pharmaceutical composition as described above. For example, *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or a cDNA encoding an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, either by itself or included within a vector, can be introduced into cells (either *in vitro* or *in vivo*) such that the cells produce native HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide. If desired, cells that have been transformed with the gene or cDNA or a vector comprising the gene or cDNA can be introduced (or re-introduced) into an individual affected with the disease. Thus, cells that, in nature, lack native *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression and activity, or have mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression and activity, or have expression of a disease-associated HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) variant,

can be engineered to express an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide or an active fragment of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide (or a different variant of an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide). In a preferred embodiment, nucleic acid encoding the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide, or an active fragment or derivative thereof, can be introduced into an expression vector, such as a viral vector, and the vector can be introduced into appropriate cells in an animal. Other gene transfer systems, including viral and nonviral transfer systems, can be used. Alternatively, nonviral gene transfer methods, such as calcium phosphate coprecipitation, mechanical techniques (*e.g.*, microinjection); membrane fusion-mediated transfer via liposomes; or direct DNA uptake, can also be used to introduce the desired nucleic acid molecule into a cell.

Alternatively, in another embodiment of the invention, a nucleic acid of the invention; a nucleic acid complementary to a nucleic acid of the invention; or a portion of such a nucleic acid (*e.g.*, an oligonucleotide as described below), can be used in "antisense" therapy, in which a nucleic acid (*e.g.*, an oligonucleotide) that specifically hybridizes to the RNA and/or genomic DNA of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is administered or generated *in situ*. The antisense nucleic acid that specifically hybridizes to the RNA and/or DNA inhibits expression of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule, *e.g.*, by inhibiting translation and/or transcription. Binding of the antisense nucleic acid can be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interaction in the major groove of the double helix.

An antisense construct of the present invention can be delivered, for example, as an expression plasmid as described above. When the plasmid is transcribed in the cell, it produces RNA that is complementary to a portion of the mRNA and/or DNA that encodes an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide. Alternatively, the antisense construct can be an oligonucleotide probe which is generated *ex vivo* and introduced

into cells; it then inhibits expression by hybridizing with the mRNA and/or genomic DNA of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. In one embodiment, the oligonucleotide probes are modified oligonucleotides that are resistant to endogenous nucleases, *e.g.* exonucleases and/or endonucleases, thereby rendering them stable *in vivo*. Exemplary nucleic acid molecules for use as antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Patent Nos. 5,176,996; 5,264,564; and 5,256,775). Additionally, general approaches to constructing oligomers useful in antisense therapy are also described, for example, by Van der Krol *et al.*, Biotechniques 6: 958-976 (1988); and Stein *et al.*, Cancer Res 48: 2659-2668 (1988). With respect to antisense DNA, oligodeoxyribonucleotides derived from the translation initiation site, *e.g.* between the -10 and +10 regions of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid sequence, are preferred.

To perform antisense therapy, oligonucleotides (RNA, cDNA or DNA) are designed that are complementary to mRNA encoding an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide. The antisense oligonucleotides bind to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA transcripts and prevent translation. Absolute complementarity, although preferred, is not required. A sequence "complementary" to a portion of an RNA, as referred to herein, indicates that a sequence has sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid, as described in detail above. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures.

The oligonucleotides used in antisense therapy can be DNA, RNA, or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotides can be modified at the base moiety, sugar

moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotides can include other appended groups such as peptides (*e.g.* for targeting host cell receptors *in vivo*), or compounds facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, Proc. Natl. Acad. Sci. USA 86: 6553-6556 (1989); Lemaitre *et al.*, Proc. Natl. Acad Sci. USA 84: 648-652 (1987); PCT International Publication No. W088/09810)) or the blood-brain barrier (see, *e.g.*, PCT International Publication No. W089/10134), or hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, BioTechniques 6: 958-976 (1988)) or intercalating agents. (See, *e.g.*, Zon, Pharm. Res. 5: 539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent).

The antisense molecules are delivered to cells that express *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS) in vivo*. A number of methods can be used for delivering antisense DNA or RNA to cells; *e.g.*, antisense molecules can be injected directly into the tissue site, or modified antisense molecules, designed to target the desired cells (*e.g.*, antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systematically. Alternatively, in a preferred embodiment, a recombinant DNA construct is utilized in which the antisense oligonucleotide is placed under the control of a strong promoter (*e.g.*, pol III or pol II). The use of such a construct to transfect target cells in the patient results in the transcription of sufficient amounts of single stranded RNAs that will form complementary base pairs with the endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* transcripts and thereby prevent translation of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art and described above. For example, a plasmid, cosmid, YAC, or viral vector can be used to prepare the recombinant DNA

construct that can be introduced directly into the tissue site. Alternatively, viral vectors can be used that selectively infect the desired tissue, in which case administration may be accomplished by another route (*e.g.*, systematically).

Endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression can also be reduced by inactivating or "knocking out" *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid sequences or their promoters using targeted homologous recombination (*e.g.*, see Smithies *et al.*, Nature 317: 230-234 (1985); Thomas and Capecchi, Cell 51: 503-512 (1987); Thompson *et al.*, Cell 5: 313-321 (1989)). For example, a mutant, non-functional *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (either the coding regions or regulatory regions of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS) in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. The recombinant DNA constructs can be directly administered or targeted to the required site *in vivo* using appropriate vectors, as described above. Alternatively, expression of non-mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be increased using a similar method: Targeted homologous recombination can be used to insert a DNA construct comprising a non-mutant, functional *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (*e.g.*, a gene having SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism), or a portion thereof, in place of a mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in the cell, as described above. In another embodiment, targeted homologous recombination can be used to insert a DNA construct comprising a nucleic acid that encodes an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide variant that differs from that present in the cell.

Alternatively, endogenous *HDAC9, HDAC9a, HDAC9*(ΔNLS), *HDAC9a*(ΔNLS), or *HDRP*(ΔNLS) expression can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (*i.e.*, the *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* promoter and/or enhancers) to form triple helical structures that prevent transcription of *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in target cells in the body. (See generally, Helene Anticancer Drug Des., 6(6): 569-84 (1991); Helene *et al.*, Ann, N.Y. Acad. Sci., 660: 27-36 (1992); and Maher, Bioassays 14(12): 807-15 (1992)). Likewise, the antisense constructs described herein, by antagonizing the normal biological activity of one of the HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) proteins, can be used in the manipulation of tissue, *e.g.*, tissue differentiation, both *in vivo* and for *ex vivo* tissue cultures. Furthermore, the antisense techniques (*e.g.*, microinjection of antisense molecules, or transfection with plasmids whose transcripts are anti-sense with regard to an *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA or gene sequence) can be used to investigate role of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) in developmental events, as well as the normal cellular function of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) in adult tissue. Such techniques can be utilized in cell culture, but can also be used in the creation of transgenic animals.

In yet another embodiment of the invention, other HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) therapeutic compounds as described herein can also be used in the treatment or prevention of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The therapeutic compounds can be delivered in a composition, as described above, or by themselves. They can be administered systemically, or can be targeted to a particular tissue. The therapeutic compounds can be produced by a variety of means, including chemical synthesis; recombinant production; *in vivo* production (*e.g.*, a transgenic animal, such as U.S. Patent No. 4,873,316 to Meade *et al.*), for example, and can be isolated using standard means such as those described herein.

A combination of any of the above methods of treatment (*e.g.*, administration of non-mutant HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide in conjunction with antisense therapy targeting mutant *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*; or *HDRP(ΔNLS)* mRNA; administration of a first variant encoded by *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in conjunction with antisense therapy targeting a second encoded by *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, can also be used.

In another embodiment, the invention is directed to *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecules and HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptides for use as a medicament in therapy. For example, the nucleic acid molecules or polypeptides of the present invention can be used in the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In addition, the *HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecules and HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptides described herein can be used in the manufacture of a medicament for the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

The invention will be further described by the following non-limiting examples. The teachings of all publications cited herein are incorporated herein by reference in their entirety.

EXEMPLIFICATION

Cloning of cDNA encodes a novel HDAC, designated HDAC9

HDAC9 was cloned by PCR and 3' rapid amplification of cDNA ends using primers designed from the sequence of human chromosome 7 whose translated product exhibited 80% identity to the HDAC domain of HDAC4, described in detail as follows.

Database analyses indicate that *HDRP* is located on chromosome 7 (7p15-p21). The human genome database (February 2001 release) of GenBank was searched using the human HDAC4 amino acid sequence. The TBLASTN program

was used to identify open reading frames downstream of *HDRP* on chromosome 7 that exhibit significant homology to the HDAC domain of HDAC4. Several fragments whose translated products exhibit over 58% identity were retrieved. Two sense primers (OL486, 5'-CCATGGAAACGGTACCCAGCAGGC-3' (SEQ ID NO: 16) and OL487, 5'-CACTCCATCGCTATGATGAAGGG-3' (SEQ ID NO: 17)) and antisense primers (OL484, 5'-AGTTCCCTTCATCATAGCGATGG-3' (SEQ ID NO: 18) and OL485, 5'-AATGTACAGGATGCTGGGGT-3' (SEQ ID NO: 19)) each were designed based upon one of these fragments whose translated products matched amino acids 842-873 of HDAC4. RT-PCR was performed using each of the antisense primers and a sense primer (5'-CCCTTGTAGCTGGTGGAGTTCCCTT-3' (SEQ ID NO: 20)) from the coding region of *HDRP* and human brain cDNA as a template. PCR was performed in a Biometra TGRADIENT Thermocycler for 30 cycles at 95°C for 20 seconds, 60°C for 20 seconds, and 72°C for 120 seconds.

3'-rapid amplification of cDNA ends was performed using the sense primer OL486 and adaptor primer 1 (Clontech), and marathon-ready cDNA from human brain (Clontech, Palo Alto, CA) according to the manufacturer's instruction. The products were re-amplified using nested sense primer OL487 and adaptor primer 2 (Clontech, Palo Alto, CA). PCR products were cloned into pGEM-T-easy vector (Promega, Madison, WI) and sequenced using an automated DNA sequencer at the DNA Sequencing Core Facility of the Memorial Sloan-Kettering Cancer Center, using DNA sequencing methods known to one of skill in the art.

Two cDNAs were cloned from the above-described methods. One cDNA (SEQ ID NO:1) encodes an HDAC9 protein that is 1011 amino acids in length. The other cDNA (SEQ ID NO: 3) encodes an HDAC9a protein that is 879 amino acids long. The cDNA sequence and amino sequence of *HDAC9* and *HDAC9a* are shown in FIGS. 1A-1G and FIGS. 2A-2B, respectively. Database analyses of these cDNAs against human genomic DNA sequences indicated that these two cDNAs are generated by alternatively splicing. An alignment of HDAC9, HDAC9a, HDRP, and HDAC4 is shown in FIGS. 3A-3C.

Each of the HDAC9 and HDAC9a nucleic acid sequences were cloned into the pFLAG-CMV-5b vector (Sigma) in frame with the C-terminal FLAG tag. Only

the coding regions plus three extra base pairs (ACC) of cDNA of the HDAC9 and HDAC9a nucleic acid sequences were included in the constructs. These constructs are referred to herein as HDAC9-FLAG and HDAC9a-FLAG, respectively. These constructs are contained in *E. coli*, and can readily be expressed. For HDAC9, the insert is 3033 bp and for HDAC9a, the insert size is 2637 bp. Both HDAC9 and HDAC9a can be released with EcoRV and BamHI (whose sites have been incorporated in the primers to obtain HDAC9 and HDAC9a coding cDNA for cloning purpose) restriction enzyme digestion.

The *HDAC9* cDNA sequences from the known 5'-end of *HDRP* cDNA to the 3'-untranslated region cloned in this study cover over 511 kb of genomic DNA on chromosome 7. As shown in FIG. 4, the coding region cDNA of *HDAC9* resides in 23 exons spanning 458 kb of genomic sequence. Exons 21, 22, and 23 are one single exon in HDAC9a, but the middle exon that is numbered exon 22 in FIG. 4, containing an in-frame stop codon, is spliced out in HDAC9. In addition, exons 12 and 13 are a single exon used by HDRP. Exon 13 is spliced as part of an intron in HDAC9 and HDAC9a.

Further analysis revealed that exon 7, which contains a nuclear localization signal (NLS) is alternatively spliced in an HDRP isoform, creating HDRP(ΔNLS). RT-PCR analyses using primers based on sequences from exon 6 and exon 14 indicate that this alternative splicing event also occurs in *HDAC9* and/or *HDAC9a*. Thus, it is possible that at least 6 proteins can be generated from a single *HDAC9* gene by alternatively splicing of its RNA. The cDNA sequences and amino acid sequences for HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), and HDRP(ΔNLS) are shown in FIGS. 1A-1O and 2A-2E, respectively.

HDAC9 mRNA is differentially expressed among human tissues

The expression of *HDAC9* mRNA was determined by Northern blot analysis using a human multiple tissue Northern blot (Clontech, Palo Alto, CA). Hybridization was performed according to the manufacturer's instruction using ExPressHyb solution (Clontech, Palo Alto, CA). The ^{32}P-random priming labeled 3'-untranslated region common to both *HDAC9* and *HDAC9a* that shares no significant sequence homology with *HDRP* was used as a probe. Two transcripts at

9.8 and 4.1 kb were detected in all tissues examined (FIG. 6A). The 4.1 kb transcript is shorter than the 4.4 kb *HDRP* transcript (See Zhou, *et al.*, Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)). A third transcript at 1.2 kb was detected in placenta (FIG. 6A). Similar to *HDRP* (See Zhou, X., *et al.*, Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)), high levels of *HDAC9* transcripts were detected in brain and skeletal muscle (FIG. 6A).

The distribution of alternatively spliced mRNA variants among tissues was examined by RT-PCR using primers (OL516 5'-TGTGTCATCGAGCTGGCTTC-3' (SEQ ID NO: 21) and OL517 5'-ATCTTCTGCAAGTGGCTCCA-3' (SEQ ID NO: 22)) spanning the alternatively spliced exon 22 and cDNA panel from the same tissues as the multiple tissue Northern blot. PCR was performed in a Biometra TGRADIENT Thermocycler for 30 cycles at 95°C for 20 seconds, 60°C for 20 seconds, and 72°C for 60 seconds. The expected sizes of PCR products were 680 base pairs for *HDAC9* and 993 base pairs for *HDAC9a*. The ratio of *HDAC9* and *HDAC9a* transcripts differed among tissues (FIG. 6B). In the placenta and kidney, the levels of the two transcripts were about the same (FIG. 6B). In the brain, heart, and pancreas, there were more transcripts of *HDAC9* than *HDAC9a*. In the other tissues examined, there were more *HDAC9a* transcripts than *HDAC9* transcripts (FIG. 6B). Under the conditions tested, *HDAC9* transcripts were undetectable in liver (FIG. 6B). The lung had an *HDAC9* product that was larger than expected and abundant. The lung also had low levels of *HDAC9* transcripts and *HDAC9a* transcripts (FIG. 6B). An additional PCR product was also amplified from cDNA of the pancreas; this product was than the expected products from *HDAC9* and *HDAC9a* (FIG. 6B). The identity of the different sized transcripts is unknown.

HDAC9 and HDAC9a possess histone deacetylase activity

HDAC9 was named based on sequence homology to HDAC4 (FIGS. 3A-3C). To determine whether HDAC9 and HDAC9a possess HDAC activity, an HDAC enzymatic assay was performed using anti-FLAG immunoprecipitated HDAC9-FLAG and HDAC9a-FLAG.

C-terminal FLAG-tagged HDAC9 (HDAC9-FLAG) and HDAC9a (HDAC9a-FLAG) expression vectors were constructed using the pFLAG-CMV-5b

vector (Sigma) and PCR amplified coding regions of HDAC9 and HDAC9a in frame with the FLAG-tag to form pFLAG-CMV-5b-HDAC9 (plasmid VR1) and pFLAG-CMV-5b-HDAC9a (plasmid VR2). All constructs were confirmed by DNA sequencing.

Transfection of human kidney 293T cells, immunoprecipitation using anti-FLAG M2 Agarose (Sigma), Western blot analyses and dual luciferase assays were performed essentially as previously described by Zhou *et al.* (Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)). Briefly, the cells (American Type Culture Collection) were cultured in DME HG medium (GIBCO/BRL) supplemented with 10% (vol/vol) FBS at 37 °C in a 5% CO_2 atmosphere. Transient transfection was performed by using Lipofectamine (GIBCO/BRL) or Fugene 6 (Roche Molecular Biochemicals) according to the manufacturers' instructions. Cells were harvested 24 to 48 hours after transfection and lysed in IP lysis buffer (50 mM Tris·HCl, pH 7.5/120 mM NaCl/5 mM EDTA/0.5% NP-40) at 5 x 10^7 cells per ml. Immunoprecipitation with anti-FLAG M2-agarose (Sigma, St. Louis, MO) was performed according to the manufacturer's instructions. Immunoprecipitated proteins were released from the agarose beads by using FLAG-peptide and either used directly for HDAC enzymatic activity assays or resolved on SDS/PAGE for Western blot analyses. Anti-FLAG antibody was purchased from Sigma (St. Louis, MO). Western blot analyses were performed using standard methods.

HDAC9 and HDAC9a enzymatic activity were assessed with the HDAC Fluorescent Activity Assay/Drug Discovery Kit-AK-500 (BIOMOL Research Laboratories) using a FLUOR DE LYS™ that contains an acetylated lysine side chain as a substrate and immunoprecipitated HDAC9-FLAG and HDAC9a-FLAG polypeptides according to the manufacturer's instruction and a SPECTRAmax® GEMINI XS microplate spectrofluorometer using the SOFTmax® PRO system (Molecular Devices) at excitation 355 nm and emission 460 nm with a cut off filter of 455 nm. Briefly, HDAC9-FLAG and HDAC9a-FLAG were incubated with the substrate overnight at room temperature in a 96-well plate. The reaction was stopped by addition of Fluor De Lys™ Developer and samples were read with the fluorometer.

As shown in FIG. 7, both HDAC9-FLAG and HDAC9a-FLAG deacetylated the acetylated lysine of FLUOR DE LYS™ and the activity of HDAC9 and HDAC9a was comparable. To examine the activity of HDAC9 and HDAC9a, inhibition studies using TSA were carried out by preincubating HDAC9-FLAG and HDAC9a-FLAG with TSA for 15 minutes at room temperature. The assay was then carried out as stated above. As shown in FIG. 7, TSA inhibited HDAC9 and HDAC9a deacetylase activity. The inset gel in FIG. 7 shows the amount of protein used in the assay. SAHA, a potent HDAC inhibitor (Richon *et al.*, Proc. Natl. Acad. Sci. USA, 95:3003-3007 (1998)) also completely inhibited the histone deacetylase activity of HDAC9-FLAG and HDAC9a-FLAG. The HDAC activity of HDAC9 and HDAC9a was about ten times lower than the deacetylase activity of HDAC4 when comparable amount of protein was used under conditions tested here.

HDAC9 and HDAC9a enzymatic activity was also determined through HDAC enzymatic assays using ^{3}H-histones isolated from murine erythroleukemia cells as a substrate. This assay was performed essentially as described by Richon *et al.* (Proc. Natl. Acad. Sci. USA, 95:3003-3007 (1998)). Briefly, HDAC9-FLAG and HDAC9a-FLAG were incubated with ^{3}H-histones overnight at 37°C. The reaction was stopped by the addition of 1M HCl/0.1 acetic acid. Released ^{3}H-acetic acid was extracted with ethyl acetate and quantified by scintillation counting. For inhibition studies, the immunoprecipitated complexes were preincubated with the different HDAC inhibitors for 30 minutes at 4°C.

As shown in FIG. 8, HDAC9a-FLAG deacetylated ^{3}H-acetyl-histones. SAHA, a potent HDAC inhibitor also completely inhibited the histone deacetylase activity of HDAC9a-FLAG. TSA also inhibited HDAC9a deacetylase activity. Similar results were obtained when HDAC9 was used as the enzyme source.

HDAC9 and HDAC9a repress MEF2-mediated transcription

The Xenopus homolog of HDRP, MITR, was identified as a MEF2 interacting transcriptional repressor (Sparrow *et al.*, EMBO J. 18:5085-5098(1999)) and mouse HDRP also interacts with and represses MEF2 mediated transcription (Zhang *et al.*, J. Biol. Chem. 276:35-39 (2001)). We first tested whether HDAC9-FLAG and HDAC9a-FLAG interact with MEF2. 293 cells were transfected with

vector, HDAC9-FLAG, or HDAC9a-FLAG. The cells were subsequently lysed and HDAC9-FLAG and HDAC9a-FLAG proteins were immunoprecipitated with anti-FLAG antibodies. Western blot analysis of the immunoprecipitated proteins was carried out, using anti-MEF-2 antibody to probe the blot. As shown in FIG. 9A, both HDAC9 and HDAC9a interacted with MEF2 in 293T cells.

It was then determined whether HDAC9 and HDAC9a repress MEF2-mediated transcription. This determination was carried out as follows. The p3XMEF2-luciferase reporter gene (100 ng) and the vector pRL-TK (Promega) (5 ng) were co-transfected into 293T cells in the absence (pcDNA3 empty vector) or presence of MEF2C (100 ng of pCMV-MEF2C). HDAC9-F (1 ng, 10 ng, or 100 ng of pFLAG-HDAC9; pFLAG-HDAC9 and HDAC9-FLAG are different constructs, with the FLAG sequence located at opposite ends of the HDAC9 nucleotide, but are functionally equivalent) or HDAC9a-F (1 ng, 10 ng, or 100 ng of pFLAG-HDAC9a; pFLAG-HDAC9a and HDAC9a-FLAG are different constructs, with the FLAG sequence located at opposite ends of the HDAC9a nucleotide, but are functionally equivalent) was included in a subset of experimental groups with the MEF2C vector. pFLAG empty vector was used to adjust the DNA to an equal amount in each transfection. The cells were harvested 24 to 36 hours after transfection and the luciferase activities were measured using the Dual-Luciferase™ Reporter Assay System from Promega according to the manufacturer's instruction. The firefly luciferase activity was first normalized to the co-transfected Renilla luciferase activity (encoded by the pRL-TK vector), and the luciferase activity value for cells transfected with MEF2C alone was set at 1. MEF2C activated transcription over 30 times the basal level of transcription. As shown in FIG. 9B, HDAC9-FLAG and HDAC9a-FLAG repressed MEF2C mediated transcriptional activation in a dose-dependent manner and completely abolished the activation at the 100 ng dose for both HDAC9 and HDAC9a. The transcriptional repression effect of HDAC9 and HDAC9a on MEF2C mediated transcription was a specific effect since a co-transfected reporter gene for transfection efficiency containing a TK promoter was not repressed by HDAC9 or HDAC9a.

Described herein is the identification and characterization of a new class II HDAC, designated HDAC9. HDAC9 has several alternatively spliced isoforms,

one of which is the previously identified HDRP (Zhou *et al.*, Proc. Natl. Acad. Sci. USA 97:1056-1061 (2000)). HDAC9 and HDAC9a possess HDAC activity, which appears to have a lower specific enzymatic activity than HDAC4. While not wishing to be bound by any particular theory, it is possible that an essential co-factor is lost during immunoprecipitation or does not exist in 293T cells (for example, metastasis-associated protein 2 is essential for the assembly of a catalytically active HDAC1 (Zhang *et al.*, Genes Dev. 13:1924-1935 (1999)), the substrates used are not its natural substrate, or the FLAG tag which interferes with the folding of the protein.

Searching the human genome with the HDAC domain from either HDAC1 or HDAC9 identified a total of 10 HDACs in the presently completed human genome sequence, a number of which are schematically represented in FIG. 10. HDACs 1, 2, 3, 8, 4, 5, 6, 7, 9, and 9a all have HDAC domains. HDRP, which is also schematically depicted in FIG. 10, does not have a catalytic domain.

All references described herein are incorporated by reference in their entirety. While this invention has been particularly shown and described with reference to preferred embodiment thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

CLAIMS

What is claimed is:

1. An isolated or recombinant histone deacetylase polypeptide, said polypeptide selected from:
   a) an isolated or recombinant polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and
   b) an isolated or recombinant polypeptide having at least 60% sequence identity with any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.

2. The isolated or recombinant histone deacetylase polypeptide of Claim 1, said polypeptide selected from:
   a) a polypeptide consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.

3. The isolated or recombinant histone deacetylase polypeptide of Claim 1, wherein said polypeptide is human.

4. An isolated nucleic acid molecule selected from the group:
   a) an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9;
   b) a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9
   c) an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10;

d) a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10;

e) a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; or

f) a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, or SEQ ID NO: 7; and

g) an isolated nucleic acid molecule that has at least 55% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof.

5. The isolated nucleic acid molecule of Claim 4, said nucleic acid molecule consisting of the nucleic acid molecule selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, and SEQ ID NO: 9.

6. The isolated nucleic acid molecule of Claim 4, wherein said nucleic acid molecule is human.

7. A vector comprising the isolated nucleic acid molecule of Claim 4.

8. A cell comprising the vector of Claim 7.

9. A cell comprising the isolated nucleic acid molecule of Claim 4.

10. A purified antibody that selectively binds a polypeptide of Claim 1.

11. A method of identifying a compound that modulates expression of a nucleic acid molecule of Claim 4, said method comprising the steps of:

a) contacting said nucleic acid molecule with a candidate compound under conditions suitable for expression; and

b) assessing the level of expression of said nucleic acid molecule,

wherein a candidate compound that increases or decreases expression of said nucleic acid molecule relative to a control is a compound that modulates expression of said nucleic acid molecule.

12. The method of Claim 11, wherein said method is carried out in a cell or animal.

13. The method of Claim 11, wherein said method is carried out in a cell free system.

14. A method of identifying a compound that modulates the enzymatic activity of the polypeptide of Claim 1, said method comprising the steps of:

a) contacting said polypeptide with a candidate compound under conditions suitable for enzymatic reaction; and

b) assessing the enzymatic activity level of said polypeptide,

wherein a candidate compound that increases or decreases the enzymatic activity level of said polypeptide relative to a control is a compound that modulates the enzymatic activity of said polypeptide.

15. The method of Claim 14, wherein said method is carried out in a cell or animal.

16. The method of Claim 14, wherein said method is carried out in a cell free system.

17. The method of Claim 14, wherein said polypeptide is further contacted with a substrate for the polypeptide, and wherein said substrate is selected from the group consisting of a cell proliferation disease binding agent, an

apoptotic disease binding agent, and a cell differentiation disease binding agent.

18. The method of Claim 17, wherein said candidate compound is an inhibitor.

19. The method of Claim 17, wherein said candidate compound is an activator.

20. A method of identifying a compound that modulates the transcriptional repression activity of the polypeptide of Claim 1, said method comprising the steps of:

a) contacting said polypeptide with a candidate compound under conditions suitable for a transcriptional repression reaction; and

b) assessing the transcriptional repression activity level of said polypeptide,

wherein a candidate compound that increases or decreases the transcriptional repression activity level of said polypeptide relative to a control is a compound that modulates the transcriptional repression activity of said polypeptide.

21. The method of Claim 20, wherein said method is carried out in a cell or animal.

22. The method of Claim 20, wherein said method is carried out in a cell free system.

23. The method of Claim 20, wherein said polypeptide is further contacted with a substrate for the polypeptide, and wherein said substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding agent.

24. The method of Claim 23, wherein said candidate compound is an inhibitor.

25. The method of Claim 23, wherein said candidate compound is an activator.

26. A method of identifying a compound that modulates expression of a nucleic acid molecule of Claim 4, said method comprising the steps of:

a) providing a nucleic acid molecule comprising a promoter region of said nucleic acid of Claim 4 or part of a promoter region of said nucleic acid of Claim 4 operably linked to a reporter gene;

b) contacting said nucleic acid molecule or with a candidate compound; and

c) assessing the level of said reporter gene,

wherein a candidate compound that increases or decreases expression of said reporter gene relative to a control is a compound that modulates expression of said nucleic acid molecule of Claim 4.

27. The method of Claim 26, wherein said method is carried out in a cell.

28. A method of identifying a polypeptide that interacts with a polypeptide of Claim 1 in a yeast two-hybrid system, said method comprising the steps of:

a) providing a first nucleic acid vector comprising a nucleic acid molecule encoding a DNA binding domain and said polypeptide of Claim 1;

b) providing a second nucleic acid vector comprising a nucleic acid encoding a transcription activation domain and a nucleic acid encoding a test polypeptide;

c) contacting said first nucleic acid vector with said second nucleic acid vector in a yeast two-hybrid system; and

d) assessing transcriptional activation in said yeast two-hybrid system,

wherein an increase in transcriptional activation relative to a control indicates that the test polypeptide is a polypeptide that interacts with said polypeptide of Claim 1.

29. A pharmaceutical composition comprising a polypeptide of Claim 1.

30. A method of diagnosing a cell proliferation disease, an apoptotic disease, or a cell differentiation disease in a subject, said method comprising the steps of:

a) obtaining a sample from said subject; and

b) assessing the level of activity or expression of said polypeptide of Claim 1 in said sample, or detecting the level of said nucleic acid molecule of Claim 4,

wherein if said level is increased relative to a control, then said subject has an increased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and wherein if said level is decreased relative to a control, then said subject has a decreased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

31. The method of Claim 30, wherein said level of activity or expression of said polypeptide of Claim 1 in said sample is measured using immunohistochemical techniques.

32. The method of Claim 30, wherein said level of said nucleic acid molecule of Claim 4 in said sample is measured using *in situ* hybridization techniques.

33. A method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, said method comprising administering a compound identified by the method of Claim 14.

34. A method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, said method comprising administering a compound identified by the method of Claim 20.

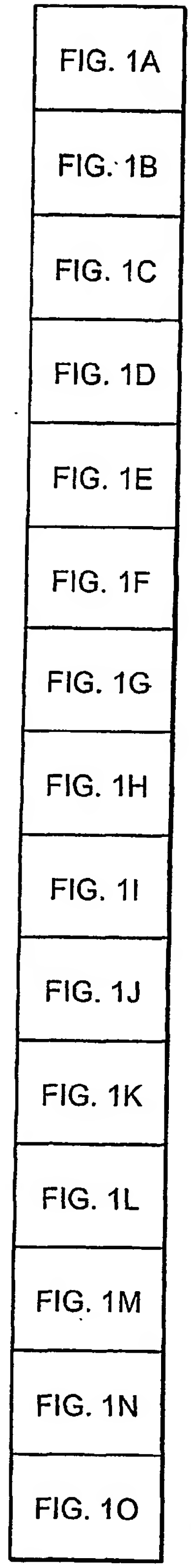


FIG. 1A
FIG. 1B
FIG. 1C
FIG. 1D
FIG. 1E
FIG. 1F
FIG. 1G
FIG. 1H
FIG. 1I
FIG. 1J
FIG. 1K
FIG. 1L
FIG. 1M
FIG. 1N
FIG. 1O

FIG. 1

HDAC9 3186 bp Coding 151-3186

Exon 1

```
1   ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca cttgcaggac tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact

                                                2
101 ctaagccaga tggggtggct ggacgagagc agctcttggc tcagcaaaga ATGCACAGTA TGATCAGCTC AGTGGATGTG AAGTCAGAAG TTCCTGTGGG

201 CCTGGAGCCC ATCTCACCTT TAGACCTAAG GACAGACCTC AGGATGATGA TGCCCGTGGT GGACCCTGTT GTCCGTGAGA AGCAATTGCA GCAGGAATTA

                       3
301 CTTCTTATCC AGCAGCAGCA ACAAATCCAG AAGCAGCTTC TGATAGCAGA GTTTCAGAAA CAGCATGAGA ACTTGACACG GCAGCACCAG GCTCAGCTTC

                                                          4
401 AGGAGCATAT CAAGGAACTT CTAGCCATAA AACAGCAACA AGAACTCCTA GAAAAGGAGC AGAAACTGGA GCAGCAGAGG CAAGAACAGG AAGTAGAGAG

501 GCATCGCAGA GAACAGCAGC TTCCTCCTCT CAGAGGCAAA GATAGAGGAC GAGAAAGGGC AGTGGCAAGT ACAGAAGTAA AGCAGAAGCT TCAAGAGTTC

                                                                    5
601 CTACTGAGTA AATCAGCAAC GAAAGACACT CCAACTAATG GAAAAAATCA TTCCGTGAGC CGCCATCCCA AGCTCTGGTA CACGGCTGCC CACCACACAT

                                   6
701 CATTGGATCA AAGCTCTCCA CCCCTTAGTG GAACATCTCC ATCCTACAAG TACACATTAC CAGGAGCACA AGATGCAAAG GATGATTTCC CCCTTCGAAA

                                                7
801 AACTGCCTCT GAGCCCAACT TGAAGGTGCG GTCCAGGTTA AAACAGAAAG TGGCAGAGAG GAGAAGCAGC CCCTTACTCA GGCGGAAGGA TGGAAATGTT
```

FIG. 1A

```
                                                           8
901  GTCACTTCAT TCAAGAAGCG AATGTTTGAG GTGACAGAAT CCTCAGTCAG TAGCAGTTCT CCAGGCTCTG GTCCCAGTTC ACCAAACAAT GGGCCAACTG
                                                                         9
1001 GAAGTGTTAC TGAAAATGAG ACTTCGGTTT TGCCCCCTAC CCCTCATGCC GAGCAAATGG TTTCACAGCA ACGCATTCTA ATTCATGAAG ATTCCATGAA

1101 CCTGCTAAGT CTTTATACCT CTCCTTCTTT GCCCAACATT ACCTTGGGGC TTCCCGCAGT GCCATCCCAG CTCAATGCTT CGAATTCACT CAAAGAAAAG

1201 CAGAAGTGTG AGACGCAGAC GCTTAGGCAA GGTGTTCCTC TGCCTGGGCA GTATGGAGGC AGCATCCCGG CATCTTCCAG CCACCCTCAT GTTACTTTAG
                                                                  10
1301 AGGGAAAGCC ACCCAACAGC AGCCACCAGG CTCTCCTGCA GCATTTATTA TTGAAAGAAC AAATGCGACA GCAAAAGCTT CTTGTAGCTG GTGGAGTTCC

1401 CTTACATCCT CAGTCTCCCT TGGCAACAAA AGAGAGAATT TCACCTGGCA TTAGAGGTAC CCACAAATTG CCCCGTCACA GACCCCTGAA CCGAACCCAG
                                                  11
1501 TCTGCACCTT TGCCTCAGAG CACGTTGGCT CAGCTGGTCA TTCAACAGCA ACACCAGCAA TTCTTGGAGA AGCAGAAGCA ATACCAGCAG CAGATCCACA

1601 TGAACAAACT GCTTTCGAAA TCTATTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGGA AGAGCTTCAG GGGGACCAGG CGATGCAGGA
                                            12
1701 AGACAGAGCG CCCTCTAGTG GCAACAGCAC TAGGAGCGAC AGCAGTGCTT GTGTGGATGA CACACTGGGA CAAGTTGGGG CTGTGAAGGT CAAGGAGGAA

1801 CCAGTGGACA GTGATGAAGA TGCTCAGATC CAGGAAATGG AATCTGGGGA GCAGGCTGCT TTTATGCAAC AGCCTTTCCT GGAACCCACG CACACACGTG
```

FIG. 1B

1901 CGCTCTCTGT GCGCCAAGCT CCGCTGGCTG CGGTTGGCAT GGATGGATTA GAGAAACACC GTCTCGTCTC CAGGACTCAC TCTTCCCCTG CTGCCTCTGT

14

2001 TTTACCTCAC CCAGCAATGG ACCGCCCCCT CCAGCCTGGC TCTGCAACTG GAATTGCCTA TGACCCCTTG ATGCTGAAAC ACCAGTGCGT TTGTGGCAAT

15

2101 TCCACCACCC ACCCTGAGCA TGCTGGACGA ATACAGAGTA TCTGGTCACG ACTGCAAGAA ACTGGGCTGC TAAATAAATG TGAGCGAATT CAAGGTCGAA

16

2201 AAGCCAGCCT GGAGGAAATA CAGCTTGTTC ATTCTGAACA TCACTCACTG TTGTATGGCA CCAACCCCCT GGACGGACAG AAGCTGGACC CCAGGATACT

17

2301 CCTAGGTGAT GACTCTCAAA AGTTTTTTTC CTCATTACCT TGTGGTGGAC TTGGGGTGGA CAGTGACACC ATTTGGAATG AGCTACACTC GTCCGGTGCT

18 19

2401 GCACGCATGG CTGTTGGCTG TGTCATCGAG CTGGCTTCCA AAGTGGCCTC AGGAGAGCTG AAGAATGGGT TTGCTGTTGT GAGGCCCCCT GGCCATCACG

20

2501 CTGAAGAATC CACAGCCATG GGGTTCTGCT TTTTTAATTC AGTTGCAATT ACCGCCAAAT ACTTGAGAGA CCAACTAAAT ATAAGCAAGA TATTGATTGT

21

2601 AGATCTGGAT GTTCACCATG GAAACGGTAC CCAGCAGGCC TTTTATGCTG ACCCCAGCAT CCTGTACATT TCACTCCATC GCTATGATGA AGGGAACTTT

23

2701 TTCCCTGGCA GTGGAGCCCC AAATGAGGTT GGAACAGGCC TTGGAGAAGG GTACAATATA AATATTGCCT GGACAGGTGG CCTTGATCCT CCCATGGGAG

24

2801 ATGTTGAGTA CCTTGAAGCA TTCAGGAcca TCGTGAAGCC TGTGGCCAAA GAGTTTGATC CAGACATGGT CTTAGTATCT GCTGGATTTG ATGCATTGGA

25

2901 AGGCCACACC CCTCCTCTAG GAGGGTACAA AGTGACGGCA AAATGTTTTG GTCATTTGAC GAAGCAATTG ATGACATTGG CTGATGGACG TGTGGTGTTG

3001 GCTCTAGAAG GAGGACATGA TCTCACAGCC ATCTGTGATG CATCAGAAGC CTGTGTAAAT GCCCTTCTAG GAAATGAGCT GGAGCCACTT GCAGAAGATA

26

3101 TTCTCCACCA AAGCCCGAAT ATGAATGCTG TTATTTCTTT ACAGAAGATC ATTGAAATTC AAAGTATGTC TTTAAAGTTC TCTTAA

FIG. 1C

HDAC9a 3499 bp (Coding 151-2790)

```
                             Exon              1
  1 ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca cttgcaggac tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact
                                               2
101 ctaagccaga tggggtggct ggacgagagc agctcttggc tcagcaaaga ATGCACAGTA TGATCAGCTC AGTGGATGTG AAGTCAGAAG TTCCTGTGGG

201 CCTGGAGCCC ATCTCACCTT TAGACCTAAG GACAGACCTC AGGATGATGA TGCCCGTGGT GGACCCTGTT GTCCGTGAGA AGCAATTGCA GCAGGAATTA
                                               3
301 CTTCTTATCC AGCAGCAGCA ACAAATCCAG AAGCAGCTTC TGATAGCAGA GTTTCAGAAA CAGCATGAGA ACTTGACACG GCAGCACCAG GCTCAGCTTC

401 AGGAGCATAT CAAGGAACTT CTAGCCATAA AACAGCAACA AGAACTCCTA GAAAAGGAGC AGAAACTGGA GCAGCAGAGG CAAGAACAGG AAGTAGAGAG
                                               4
501 GCATCGCAGA GAACAGCAGC TTCCTCCTCT CAGAGGCAAA GATAGAGGAC GAGAAAGGGC AGTGGCAAGT ACAGAAGTAA AGCAGAAGCT TCAAGAGTTC
```

FIG. 1D

```
                                                   5
601  CTACTGAGTA AATCAGCAAC GAAAGACACT CCAACTAATG GAAAAAATCA TTCCGTGAGC CGCCATCCCA AGCTCTGGTA CACGGCTGCC CACCACACAT
                                                   6
701  CATTGGATCA AAGCTCTCCA CCCCTTAGTG GAACATCTCC ATCCTACAAG TACACATTAC CAGGAGCACA AGATGCAAAG GATGATTTCC CCCTTCGAAA
                                                   7
801  AACTGCCTCT GAGCCCAACT TGAAGGTGCG GTCCAGGTTA AAACAGAAAG TGGCAGAGAG GAGAAGCAGC CCCTTACTCA GGCGGAAGGA TGGAAATGTT

901  GTCACTTCAT TCAAGAAGCG AATGTTTGAG GTGACAGAAT CCTCAGTCAG TAGCAGTTCT CCAGGCTCTG GTCCCAGTTC ACCAAACAAT GGGCCAACTG
                                                   8
1001 GAAGTGTTAC TGAAAATGAG ACTTCGGTTT TGCCCCCTAC CCCTCATGCC GAGCAAATGG TTTCACAGCA ACGCATTCTA ATTCATGAAG ATTCCATGAA
                                                   9
1101 CCTGCTAAGT CTTTATACCT CTCCTTCTTT GCCCAACATT ACCTTGGGGC TTCCCGCAGT GCCATCCCAG CTCAATGCTT CGAATTCACT CAAAGAAAAG

1201 CAGAAGTGTG AGACGCAGAC GCTTAGGCAA GGTGTTCCTC TGCCTGGGCA GTATGGAGGC AGCATCCCGG CATCTTCCAG CCACCCTCAT GTTACTTTAG
                                                   10
1301 AGGGAAAGCC ACCCAACAGC AGCCACCAGG CTCTCCTGCA GCATTTATTA TTGAAAGAAC AAATGCGACA GCAAAAGCTT CTTGTAGCTG GTGGAGTTCC

1401 CTTACATCCT CAGTCTCCCT TGGCAACAAA AGAGAGAATT TCACCTGGCA TTAGAGGTAC CCACAAATTG CCCCGTCACA GACCCCTGAA CCGAACCCAG
                                                   11
1501 TCTGCACCTT TGCCTCAGAG CACGTTGGCT CAGCTGGTCA TTCAACAGCA ACACCAGCAA TTCTTGGAGA AGCAGAAGCA ATACCAGCAG CAGATCCACA
```

FIG. 1E

1601 TGAACAAACT GCTTTCGAAA TCTATTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGGA AGAGCTTCAG GGGGACCAGG CGATGCAGGA

12

1701 AGACAGAGCG CCCTCTAGTG GCAACAGCAC TAGGAGCGAC AGCAGTGCTT GTGTGGATGA CACACTGGGA CAAGTTGGGG CTGTGAAGGT CAAGGAGGAA

1801 CCAGTGGACA GTGATGAAGA TGCTCAGATC CAGGAAATGG AATCTGGGGA GCAGGCTGCT TTTATGCAAC AGCCTTTCCT GGAACCCACG CACACACGTG

14

1901 CGCTCTCTGT GCGCCAAGCT CCGCTGGCTG CGGTTGGCAT GGATGGATTA GAGAAACACC GTCTCGTCTC CAGGACTCAC TCTTCCCCTG CTGCCTCTGT

2001 TTTACCTCAC CCAGCAATGG ACCGCCCCCT CCAGCCTGGC TCTGCAACTG GAATTGCCTA TGACCCCTTG ATGCTGAAAC ACCAGTGCGT TTGTGGCAAT

15

2101 TCCACCACCC ACCCTGAGCA TGCTGGACGA ATACAGAGTA TCTGGTCACG ACTGCAAGAA ACTGGGCTGC TAAATAAATG TGAGCGAATT CAAGGTCGAA

16

2201 AAGCCAGCCT GGAGGAAATA CAGCTTGTTC ATTCTGAACA TCACTCACTG TTGTATGGCA CCAACCCCCT GGACGGACAG AAGCTGGACC CCAGGATACT

17

2301 CCTAGGTGAT GACTCTCAAA AGTTTTTTTC CTCATTACCT TGTGGTGGAC TTGGGGTGGA CAGTGACACC ATTTGGAATG AGCTACACTC GTCCGGTGCT

18 19

2401 GCACGCATGG CTGTTGGCTG TGTCATCGAG CTGGCTTCCA AAGTGGCCTC AGGAGAGCTG AAGAATGGGT TTGCTGTTGT GAGGCCCCCT GGCCATCACG

20

2501 CTGAAGAATC CACAGCCATG GGGTTCTGCT TTTTTAATTC AGTTGCAATT ACCGCCAAAT ACTTGAGAGA CCAACTAAAT ATAAGCAAGA TATTGATTGT

FIG. 1F

```
                                            21
2601 AGATCTGGAT GTTCACCATG GAAACGGTAC CCAGCAGGCC TTTTATGCTG ACCCCAGCAT CCTGTACATT TCACTCCATC GCTATGATGA AGGGAACTTT

2701 TTCCCTGGCA GTGGAGCCCC AAATGAGGTT CGGTTTATTT CTTTAGAGCC CCACTTTTAT TTGTATCTTT CAGGTAATTG CATTGCATGA  ttacccctaa
                                                                                                STOP CODON
                                            22
2801 ttttcttgtc ctttgctggt gttttaaatt acacgagatt actgaattgt cccatgggac caagaaccag tgcagaacaa gtgcataacc cagagcactg

2901 tttgtcaggg aaggttgggc tgatttgatg tgttgtttga tgtttatttc aagagctccc atgtgcttgt tttcctctct tcttgctttc ttccatttgc
                                            23
3001 tctcttctct gcccaccgtg gtgtgtcttt ctcttcccag gttggaacag gccttggaga agggtacaat ataaatattg cctggacagg tggccttgat

3101 cctcccatgg gagatgttga gtaccttgaa gcattcagga ccatcgtgaa gcctgtggcc aaagagtttg atccagacat ggtcttagta tctgctggat
                                            24
3201 ttgatgcatt ggaaggccac acccctcctc taggagggta caaagtgacg gcaaaatgtt ttggtcattt gacgaagcaa ttgatgacat tggctgatgg
                                            25
3301 acgtgtggtg ttggctctag aaggaggaca tgatctcaca gccatctgtg atgcatcaga agcctgtgta aatgcccttc taggaaatga gctggagcca
                                            26
3401 cttgcagaag atattctcca ccaaagcccg aatatgaatg ctgttatttc tttacagaag atcattgaaa ttcaaagtat gtctttaaag ttctcttaa
```

FIG. 1G

```
>HDRP (deltaNLS)
   1 ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca
  51 cttgcaggac tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact
 101 ctaagccaga tggggtggct ggacgagagc agctcttggc tcagcaaaga
 151 atgcacagta tgatcagctc agtggatgtg aagtcagaag ttcctgtggg
 201 cctggagccc atctcacctt tagacctaag gacagacctc aggatgatga
 251 tgcccgtggt ggaccctgtt gtccgtgaga agcaattgca gcaggaatta
 301 cttcttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga
 351 gtttcagaaa cagcatgaga acttgacacg gcagcaccag gctcagcttc
 401 aggagcatat caaggaactt ctagccataa aacagcaaca agaactccta
 451 gaaaaggagc agaaactgga gcagcagagg caagaacagg aagtagagag
 501 gcatcgcaga gaacagcagc ttcctcctct cagaggcaaa gatagaggac
 551 gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc
 601 ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca
 651 ttccgtgagc cgccatccca agctctggta cacggctgcc caccacacat
 701 cattggatca aagctctcca ccccttagtg gaacatctcc atcctacaag
 751 tacacattac caggagcaca agatgcaaag gatgatttcc cccttcgaaa
 801 aactgaatcc tcagtcagta gcagttctcc aggctctggt cccagttcac
 851 caaacaatgg gccaactgga agtgttactg aaaatgagac ttcggttttg
 901 cccccctaccc ctcatgccga gcaaatggtt tcacagcaac gcattctaat
 951 tcatgaagat tccatgaacc tgctaagtct ttatacctct ccttctttgc
1001 ccaacattac cttggggctt cccgcagtgc catcccagct caatgcttcg
```

FIG. 1H

```
1051  aattcactca aagaaaagca gaagtgtgag acgcagacgc ttaggcaagg
1101  tgttcctctg cctgggcagt atggaggcag catcccggca tcttccagcc
1151  accctcatgt tactttagag ggaaagccac ccaacagcag ccaccaggct
1201  ctcctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct
1251  tgtagctggt ggagttccct tacatcctca gtctcccttg gcaacaaaag
1301  agagaatttc acctggcatt agaggtaccc acaaattgcc ccgtcacaga
1351  cccctgaacc gaacccagtc tgcacctttg cctcagagca cgttggctca
1401  gctggtcatt caacagcaac accagcaatt cttggagaag cagaagcaat
1451  accagcagca gatccacatg aacaaactgc tttcgaaatc tattgaacaa
1501  ctgaagcaac caggcagtca ccttgaggaa gcagaggaag agcttcaggg
1551  ggaccaggcg atgcaggaag acagagcgcc ctctagtggc aacagcacta
1601  ggagcgacag cagtgcttgt gtggatgaca cactgggaca agttggggct
1651  gtgaaggtca aggaggaacc agtggacagt gatgaagatg ctcagatcca
1701  ggaaatggaa tctggggagc aggctgcttt tatgcaacag gtaataggca
1751  aagatttagc tccaggattt gtaattaaag tcattatctg a
```

FIG. 1I

>HDAC9 (deltaNLS)

```
   1 ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca
  51 cttgcaggac tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact
 101 ctaagccaga tggggtggct ggacgagagc agctcttggc tcagcaaaga
 151 atgcacagta tgatcagctc agtggatgtg aagtcagaag ttcctgtggg
 201 cctggagccc atctcacctt tagacctaag gacagacctc aggatgatga
 251 tgcccgtggt ggaccctgtt gtccgtgaga agcaattgca gcaggaatta
 301 cttcttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga
 351 gtttcagaaa cagcatgaga acttgacacg gcagcaccag gctcagcttc
 401 aggagcatat caaggaactt ctagccataa aacagcaaca agaactccta
 451 gaaaaggagc agaaactgga gcagcagagg caagaacagg aagtagagag
 501 gcatcgcaga gaacagcagc ttcctcctct cagaggcaaa gatagaggac
 551 gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc
 601 ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca
 651 ttccgtgagc cgccatccca agctctggta cacggctgcc caccacacat
 701 cattggatca aagctctcca ccccttagtg gaacatctcc atcctacaag
 751 tacacattac caggagcaca agatgcaaag gatgatttcc cccttcgaaa
 801 aactgaatcc tcagtcagta gcagttctcc aggctctggt cccagttcac
 851 caaacaatgg gccaactgga agtgttactg aaaatgagac ttcggttttg
 901 ccccctaccc ctcatgccga gcaaatggtt tcacagcaac gcattctaat
 951 tcatgaagat tccatgaacc tgctaagtct ttatacctct ccttctttgc
1001 ccaacattac cttggggctt cccgcagtgc catcccagct caatgcttcg
1051 aattcactca aagaaaagca gaagtgtgag acgcagacgc ttaggcaagg
1101 tgttcctctg cctgggcagt atggaggcag catcccggca tcttccagcc
```

FIG. 1J

```
1151  accctcatgt tactttagag ggaaagccac ccaacagcag ccaccaggct
1201  ctcctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct
1251  tgtagctggt ggagttccct tacatcctca gtctcccttg gcaacaaaag
1301  agagaatttc acctggcatt agaggtaccc acaaattgcc ccgtcacaga
1351  cccctgaacc gaacccagtc tgcacctttg cctcagagca cgttggctca
1401  gctggtcatt caacagcaac accagcaatt cttggagaag cagaagcaat
1451  accagcagca gatccacatg aacaaactgc tttcgaaatc tattgaacaa
1501  ctgaagcaac caggcagtca ccttgaggaa gcagaggaag agcttcaggg
1551  ggaccaggcg atgcaggaag acagagcgcc ctctagtggc aacagcacta
1601  ggagcgacag cagtgcttgt gtggatgaca cactgggaca agttggggct
1651  gtgaaggtca aggaggaacc agtggacagt gatgaagatg ctcagatcca
1701  ggaaatggaa tctggggagc aggctgcttt tatgcaacag cctttcctgg
1751  aacccacgca cacacgtgcg ctctctgtgc gccaagctcc gctggctgcg
1801  gttggcatgg atggattaga gaaacaccgt ctcgtctcca ggactcactc
1851  ttcccctgct gcctctgttt tacctcaccc agcaatggac cgcccccctcc
1901  agcctggctc tgcaactgga attgcctatg accccttgat gctgaaacac
1951  cagtgcgttt gtggcaattc caccacccac cctgagcatg ctggacgaat
2001  acagagtatc tggtcacgac tgcaagaaac tgggctgcta aataaatgtg
2051  agcgaattca aggtcgaaaa gccagcctgg aggaaataca gcttgttcat
2101  tctgaacatc actcactgtt gtatggcacc aacccccctgg acggacagaa
2151  gctggacccc aggatactcc taggtgatga ctctcaaaag tttttttcct
2201  cattaccttg tggtggactt ggggtggaca gtgacaccat ttggaatgag
2251  ctacactcgt ccggtgctgc acgcatggct gttggctgtg tcatcgagct
2301  ggcttccaaa gtggcctcag gagagctgaa gaatgggttt gctgttgtga
2351  ggccccctgg ccatcacgct gaagaatcca cagccatggg gttctgcttt
2401  tttaattcag ttgcaattac cgccaaatac ttgagagacc aactaaatat
```

FIG. 1K

```
2451  aagcaagata ttgattgtag atctggatgt tcaccatgga aacggtaccc
2501  agcaggcctt ttatgctgac cccagcatcc tgtacatttc actccatcgc
2551  tatgatgaag ggaacttttt ccctggcagt ggagccccaa atgaggttgg
2601  aacaggcctt ggagaagggt acaatataaa tattgcctgg acaggtggcc
2651  ttgatcctcc catgggagat gttgagtacc ttgaagcatt caggaccatc
2701  gtgaagcctg tggccaaaga gtttgatcca gacatggtct tagtatctgc
2751  tggatttgat gcattggaag gccacacccc tcctctagga gggtacaaag
2801  tgacggcaaa atgttttggt catttgacga agcaattgat gacattggct
2851  gatggacgtg tggtgttggc tctagaagga ggacatgatc tcacagccat
2901  ctgtgatgca tcagaagcct gtgtaaatgc ccttctagga aatgagctgg
2951  agccacttgc agaagatatt ctccaccaaa gcccgaatat gaatgctgtt
3001  atttctttac agaagatcat tgaaattcaa agtatgtctt taaagttctc
3051  ttaa
```

FIG. 1L

```
>HDAC9a (deltaNLS)
   1  ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca
  51  cttgcaggac tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact
 101  ctaagccaga tggggtggct ggacgagagc agctcttggc tcagcaaaga
 151  atgcacagta tgatcagctc agtggatgtg aagtcagaag ttcctgtggg
 201  cctggagccc atctcacctt tagacctaag gacagacctc aggatgatga
 251  tgcccgtggt ggaccctgtt gtccgtgaga agcaattgca gcaggaatta
 301  cttcttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga
 351  gtttcagaaa cagcatgaga acttgacacg gcagcaccag gctcagcttc
 401  aggagcatat caaggaactt ctagccataa aacagcaaca agaactccta
 451  gaaaaggagc agaaactgga gcagcagagg caagaacagg aagtagagag
 501  gcatcgcaga gaacagcagc ttcctcctct cagaggcaaa gatagaggac
 551  gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc
 601  ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca
 651  ttccgtgagc cgccatccca agctctggta cacggctgcc caccacacat
 701  cattggatca aagctctcca ccccttagtg gaacatctcc atcctacaag
 751  tacacattac caggagcaca agatgcaaag gatgatttcc cccttcgaaa
 801  aactgaatcc tcagtcagta gcagttctcc aggctctggt cccagttcac
 851  caaacaatgg gccaactgga agtgttactg aaaatgagac ttcggttttg
 901  cccccctaccc ctcatgccga gcaaatggtt tcacagcaac gcattctaat
 951  tcatgaagat tccatgaacc tgctaagtct ttatacctct ccttctttgc
1001  ccaacattac cttggggctt cccgcagtgc catcccagct caatgcttcg
1051  aattcactca aagaaaagca gaagtgtgag acgcagacgc ttaggcaagg
1101  tgttcctctg cctgggcagt atggaggcag catcccggca tcttccagcc
1151  accctcatgt tactttagag ggaaagccac ccaacagcag ccaccaggct
```

FIG. 1M

1201	ctcctgcagc	atttattatt	gaaagaacaa	atgcgacagc	aaaagcttct
1251	tgtagctggt	ggagttccct	tacatcctca	gtctcccttg	gcaacaaaag
1301	agagaatttc	acctggcatt	agaggtaccc	acaaattgcc	ccgtcacaga
1351	cccctgaacc	gaacccagtc	tgcacctttg	cctcagagca	cgttggctca
1401	gctggtcatt	caacagcaac	accagcaatt	cttggagaag	cagaagcaat
1451	accagcagca	gatccacatg	aacaaactgc	tttcgaaatc	tattgaacaa
1501	ctgaagcaac	caggcagtca	ccttgaggaa	gcagaggaag	agcttcaggg
1551	ggaccaggcg	atgcaggaag	acagagcgcc	ctctagtggc	aacagcacta
1601	ggagcgacag	cagtgcttgt	gtggatgaca	cactgggaca	agttggggct
1651	gtgaaggtca	aggaggaacc	agtggacagt	gatgaagatg	ctcagatcca
1701	ggaaatggaa	tctggggagc	aggctgcttt	tatgcaacag	cctttcctgg
1751	aacccacgca	cacacgtgcg	ctctctgtgc	gccaagctcc	gctggctgcg
1801	gttggcatgg	atggattaga	gaaacaccgt	ctcgtctcca	ggactcactc
1851	ttcccctgct	gcctctgttt	tacctcaccc	agcaatggac	cgccccctcc
1901	agcctggctc	tgcaactgga	attgcctatg	accccttgat	gctgaaacac
1951	cagtgcgttt	gtggcaattc	caccacccac	cctgagcatg	ctggacgaat
2001	acagagtatc	tggtcacgac	tgcaagaaac	tgggctgcta	aataaatgtg
2051	agcgaattca	aggtcgaaaa	gccagcctgg	aggaaataca	gcttgttcat
2101	tctgaacatc	actcactgtt	gtatggcacc	aaccccctgg	acggacagaa
2151	gctggacccc	aggatactcc	taggtgatga	ctctcaaaag	tttttttcct
2201	cattaccttg	tggtggactt	ggggtggaca	gtgacaccat	ttggaatgag
2251	ctacactcgt	ccggtgctgc	acgcatggct	gttggctgtg	tcatcgagct
2301	ggcttccaaa	gtggcctcag	gagagctgaa	gaatgggttt	gctgttgtga
2351	ggccccctgg	ccatcacgct	gaagaatcca	cagccatggg	gttctgcttt
2401	tttaattcag	ttgcaattac	cgccaaatac	ttgagagacc	aactaaatat

FIG. 1N

```
2451 aagcaagata ttgattgtag atctggatgt tcaccatgga aacggtaccc
2501 agcaggcctt ttatgctgac cccagcatcc tgtacatttc actccatcgc
2551 tatgatgaag ggaacttttt ccctggcagt ggagccccaa atgaggttcg
2601 gtttatttct ttagagcccc acttttattt gtatctttca ggtaattgca
2651 ttgcatgatt accccctaatt ttcttgtcct ttgctggtgt tttaaattac
2701 acgagattac tgaattgtcc catgggacca agaaccagtg cagaacaagt
2751 gcataaccca gagcactgtt tgtcagggaa ggttgggctg atttgatgtg
2801 ttgtttgatg tttatttcaa gagctcccat gtgcttgttt tcctctcttc
2851 ttgctttctt ccatttgctc tcttctctgc ccaccgtggt gtgtctttct
2901 cttcccaggt tggaacaggc cttggagaag ggtacaatat aaatattgcc
2951 tggacaggtg gccttgatcc tcccatggga gatgttgagt accttgaagc
3001 attcaggacc atcgtgaagc ctgtggccaa agagtttgat ccagacatgg
3051 tcttagtatc tgctggattt gatgcattgg aaggccacac ccctcctcta
3101 ggagggtaca aagtgacggc aaaatgtttt ggtcatttga cgaagcaatt
3151 gatgacattg gctgatggac gtgtggtgtt ggctctagaa ggaggacatg
3201 atctcacagc catctgtgat gcatcagaag cctgtgtaaa tgcccttcta
3251 ggaaatgagc tggagccact tgcagaagat attctccacc aaagcccgaa
3301 tatgaatgct gttatttctt tacagaagat cattgaaatt caaagtatgt
3351 ctttaaagtt ctcttaa
```

FIG. 1O

FIG. 2A
FIG. 2B
FIG. 2C
FIG. 2D
FIG. 2E

FIG. 2

```
>HDAC9 (1011 amino acids)
MHSMISSVDVKSEVPVGLEPISPLDLRTDLRMMMPVVDPVVREKQLQQELLLIQQQQQI
QKQLLIAEFQKQHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQKLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTASEPNLKVRSRLKQKVAE
RRSSPLLRRKDGNVVTSFKKRMFEVTESSVSSSSPGSGPSSPNNGPTGSVTENETSVLP
PTPHAEQMVSQQRILIHEDSMNLLSLYTSPSLPNITLGLPAVPSQLNASNSLKEKQKCE
TQTLRQGVPLPGQYGGSIPASSSHPHVTLEGKPPNSSHQALLQHLLLKEQMRQQKLLVA
GGVPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQSAPLPQSTLAQLVIQQQHQQFL
EKQKQYQQQIHMNKLLSKSIEQLKQPGSHLEEAEEELQGDQAMQEDRAPSSGNSTRSDS
SACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMESGEQAAFMQQPFLEPTHTRALSVRQA
PLAAVGMDGLEKHRLVSRTHSSPAASVLPHPAMDRPLQPGSATGIAYDPLMLKHQCVCG
NSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKASLEEIQLVHSEHHSLLYGTNPLD
GQKLDPRILLGDDSQKFFSSLPCGGLGVDSDTIWNELHSSGAARMAVGCVIELASKVAS
GELKNGFAVVRPPGHHAEESTAMGFCFFNSVAITAKYLRDQLNISKILIVDLDVHHGNG
TQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVGTGLGEGYNINIAWTGGLDPPMGDV
EYLEAFRTIVKPVAKEFDPDMVLVSAGFDALEGHTPPLGGYKVTAKCFGHLTKQLMTLA
DGRVVLALEGGHDLTAICDASEACVNALLGNELEPLAEDILHQSPNMNAVISLQKIIEI
QSMSLKFS
```

FIG. 2A

>HDAC9a (879 amino acids)
MHSMISSVDVKSEVPVGLEPISPLDLRTDLRMMMPVVDPVVREKQLQQELLLIQQQQQI
QKQLLIAEFQKQHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQKLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTASEPNLKVRSRLKQKVAE
RRSSPLLRRKDGNVVTSFKKRMFEVTESSVSSSSPGSGPSSPNNGPTGSVTENETSVLP
PTPHAEQMVSQQRILIHEDSMNLLSLYTSPSLPNITLGLPAVPSQLNASNSLKEKQKCE
TQTLRQGVPLPGQYGGSIPASSSHPHVTLEGKPPNSSHQALLQHLLLKEQMRQQKLLVA
GGVPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQSAPLPQSTLAQLVIQQQHQQFL
EKQKQYQQQIHMNKLLSKSIEQLKQPGSHLEEAEEELQGDQAMQEDRAPSSGNSTRSDS
SACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMESGEQAAFMQQPFLEPTHTRALSVRQA
PLAAVGMDGLEKHRLVSRTHSSPAASVLPHPAMDRPLQPGSATGIAYDPLMLKHQCVCG
NSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKASLEEIQLVHSEHHSLLYGTNPLD
GQKLDPRILLGDDSQKFFSSLPCGGLGVDSDTIWNELHSSGAARMAVGCVIELASKVAS
GELKNGFAVVRPPGHHAEESTAMGFCFFNSVAITAKYLRDQLNISKILIVDLDVHHGNG
TQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVRFISLEPHFYLYLSGNCIA

FIG. 2B

>HDAC9 (ΔNLS) (967 amino acids)

MHSMISSVDVKSEVPVGLEPISPLDLRTDLRMMMPVVDPVVREKQLQQELLLIQQQQQI
QKQLLIAEFQKQHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQKLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTESSVSSSSPGSGPSSPNN
GPTGSVTENETSVLPPTPHAEQMVSQQRILIHEDSMNLLSLYTSPSLPNITLGLPAVPS
QLNASNSLKEKQKCETQTLRQGVPLPGQYGGSIPASSSHPHVTLEGKPPNSSHQALLQH
LLLKEQMRQQKLLVAGGVPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQSAPLPQS
TLAQLVIQQQHQQFLEKQKQYQQQIHMNKLLSKSIEQLKQPGSHLEEAEEELQGDQAMQ
EDRAPSSGNSTRSDSSACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMESGEQAAFMQQP
FLEPTHTRALSVRQAPLAAVGMDGLEKHRLVSRTHSSPAASVLPHPAMDRPLQPGSATG
IAYDPLMLKHQCVCGNSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKASLEEIQLV
HSEHHSLLYGTNPLDGQKLDPRILLGDDSQKFFSSLPCGGLGVDSDTIWNELHSSGAAR
MAVGCVIELASKVASGELKNGFAVVRPPGHHAEESTAMGFCFFNSVAITAKYLRDQLNI
SKILIVDLDVHHGNGTQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVGTGLGEGYNI
NIAWTGGLDPPMGDVEYLEAFRTIVKPVAKEFDPDMVLVSAGFDALEGHTPPLGGYKVT
AKCFGHLTKQLMTLADGRVVLALEGGHDLTAICDASEACVNALLGNELEPLAEDILHQS
PNMNAVISLQKIIEIQSMSLKFS

FIG. 2C

>HDAC9a (ΔNLS) (835 amino acids)
MHSMISSVDVKSEVPVGLEPISPLDLRTDLRMMMPVVDPVVREKQLQQELLLIQQQQQI
QKQLLIAEFQKQHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQKLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTESSVSSSSPGSGPSSPNN
GPTGSVTENETSVLPPTPHAEQMVSQQRILIHEDSMNLLSLYTSPSLPNITLGLPAVPS
QLNASNSLKEKQKCETQTLRQGVPLPGQYGGSIPASSSHPHVTLEGKPPNSSHQALLQH
LLLKEQMRQQKLLVAGGVPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQSAPLPQS
TLAQLVIQQQHQQFLEKQKQYQQQIHMNKLLSKSIEQLKQPGSHLEEAEEELQGDQAMQ
EDRAPSSGNSTRSDSSACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMESGEQAAFMQQP
FLEPTHTRALSVRQAPLAAVGMDGLEKHRLVSRTHSSPAASVLPHPAMDRPLQPGSATG
IAYDPLMLKHQCVCGNSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKASLEEIQLV
HSEHHSLLYGTNPLDGQKLDPRILLGDDSQKFFSSLPCGGLGVDSDTIWNELHSSGAAR
MAVGCVIELASKVASGELKNGFAVVRPPGHHAEESTAMGFCFFNSVAITAKYLRDQLNI
SKILIVDLDVHHGNGTQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVRFISLEPHFY
LYLSGNCIA

FIG. 2D

>HDRPa (HDRP ΔNLS)(546 amino acids)

MHSMISSVDVKSEVPVGLEPISPLDLRTDLRMMMPVVDPVVREKQLQQELLLIQQQQQI
QKQLLIAEFQKQHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQKLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTESSVSSSSPGSGPSSPNN
GPTGSVTENETSVLPPTPHAEQMVSQQRILIHEDSMNLLSLYTSPSLPNITLGLPAVPS
QLNASNSLKEKQKCETQTLRQGVPLPGQYGGSIPASSSHPHVTLEGKPPNSSHQALLQH
LLLKEQMRQQKLLVAGGVPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQSAPLPQS
TLAQLVIQQQHQQFLEKQKQYQQQIHMNKLLSKSIEQLKQPGSHLEEAEEELQGDQAMQ
EDRAPSSGNSTRSDSSACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMESGEQAAFMQQV
IGKDLAPGFVIKVII

FIG. 2E

FIG. 3A
FIG. 3B
FIG. 3C

FIG. 3

FIG. 3A

```
HDRP      1   ------------------------MHSMISSVDVKSEVPVGLEP-ISPLDLRTDLRMMMP
HDAC9a    1   ------------------------MHSMISSVDVKSEVPVGLEP-ISPLDLRTDLRMMMP
HDAC9     1   ------------------------MHSMISSVDVKSEVPVGLEP-ISPLDLRTDLRMMMP
HDAC4     1   MSSQSHPDGLSGRDQPVELLNPARVNHMPSTVDVATALPLQVAPSAVPMDLRLDHQFSLP

HDRP     36   VVDPVVREKQLQQELLLIQQQQQIQKQLLIAEFQKQHENLTRQHQAQLQEHIK---ELLA
HDAC9a   36   VVDPVVREKQLQQELLLIQQQQQIQKQLLIAEFQKQHENLTRQHQAQLQEHIK---ELLA
HDAC9    36   VVDPVVREKQLQQELLLIQQQQQIQKQLLIAEFQKQHENLTRQHQAQLQEHIK---ELLA
HDAC4    61   VAEPALREQQLQQELLALKQKQQIQRQILIAEFQRQHEQLSRQHEAQLHEHIKQQQEMLA

HDRP     93   IKQQQELLEKEQKLEQQRQEQEVERHRREQQLPPLRGKDRGRERAVASTEVKQKLQEFLL
HDAC9a   93   IKQQQELLEKEQKLEQQRQEQEVERHRREQQLPPLRGKDRGRERAVASTEVKQKLQEFLL
HDAC9    93   IKQQQELLEKEQKLEQQRQEQEVERHRREQQLPPLRGKDRGRERAVASTEVKQKLQEFLL
HDAC4   121   MKHQQELLEHQRKLERHRQEQELEKQHREQKLQQLKNKEKGKESAVASTEVKMKLQEFVL

HDRP    153   SKSATKDTPTNGKNHSVSRHPKLWYTAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDD
HDAC9a  153   SKSATKDTPTNGKNHSVSRHPKLWYTAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDD
HDAC9   153   SKSATKDTPTNGKNHSVSRHPKLWYTAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDD
HDAC4   181   NK--KKALAHRNLNHCISSDPRYWYGKTQHSSLDQSSPPQSGVSTSYNHPVLGMYDAKDD

HDRP    213   FPLRKTASEPNLKVRSRLKQKVAERRSSPLLRRKDGNVVTSFKKRMFEVTESSVSSSSPG
HDAC9a  213   FPLRKTASEPNLKVRSRLKQKVAERRSSPLLRRKDGNVVTSFKKRMFEVTESSVSSSSPG
HDAC9   213   FPLRKTASEPNLKVRSRLKQKVAERRSSPLLRRKDGNVVTSFKKRMFEVTESSVSSSSPG
HDAC4   239   FPLRKTASEPNLKLRSRLKQKVAERRSSPLLRRKDGPVVTALKKRPLDVTDSACSS-APG
```

```
HDRP     273  SGPSSPNNGPTGSVTENETSVLPPTPHAEQMVSQQRILIHEDSMNLLSLYTSPSLPNITL
HDAC9a   273  SGPSSPNNGPTGSVTENETSVLPPTPHAEQMVSQQRILIHEDSMNLLSLYTSPSLPNITL
HDAC9    273  SGPSSPNNGPTGSVTENETSVLPPTPHAEQMVSQQRILIHEDSMNLLSLYTSPSLPNITL
HDAC4    298  SGPSSPNNSSGSVSAENGIAPAVPSIPAETSLAHR-LVAREGSAAPLPLYTSPSLPNITL

HDRP     333  GLPAVPSQLNASNSLKEKQKCETQTLRQGVPLPGQYGGSIPASSSHPHVTLEGKPPNSSH
HDAC9a   333  GLPAVPSQLNASNSLKEKQKCETQTLRQGVPLPGQYGGSIPASSSHPHVTLEGKPPNSSH
HDAC9    333  GLPAVPSQLNASNSLKEKQKCETQTLRQGVPLPGQYGGSIPASSSHPHVTLEGKPPNSSH
HDAC4    357  GLPATGPSAGTAGQQ-DTERLTLPALQQRLSLFPGTHLTPYLSTS--PLERDG---GAAH

HDRP     393  QALLQHLLLKEQMRQQKLLVAGG--VPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQ
HDAC9a   393  QALLQHLLLKEQMRQQKLLVAGG--VPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQ
HDAC9    393  QALLQHLLLKEQMRQQKLLVAGG--VPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQ
HDAC4    411  SPLLQHMVLLEQPPAQAPLVTGLGALPLHAQS-LVGADRVSP---SIHKLRQHRPLGRTQ

HDRP     451  SAPLPQ--STLAQLVIQQQHQQFLEKQKQ--YQQQIHMNKLLSKSIEQLKQPGSHLEEAE
HDAC9a   451  SAPLPQ--STLAQLVIQQQHQQFLEKQKQ--YQQQIHMNKLLSKSIEQLKQPGSHLEEAE
HDAC9    451  SAPLPQ--STLAQLVIQQQHQQFLEKQKQ--YQQQIHMNKLLSKSIEQLKQPGSHLEEAE
HDAC4    467  SAPLPQNAQALQHLVIQQQHQQFLEKHKQQFQQQQLQMNKIIPKPSEPARQPESHPEETE

HDRP     507  EELQGDQAMQEDRAPSSGNSTR-SDSSACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMES
HDAC9a   507  EELQGDQAMQEDRAPSSGNSTR-SDSSACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMES
HDAC9    507  EELQGDQAMQEDRAPSSGNSTR-SDSSACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMES
HDAC4    527  EELREHQALLDEPYLDRLPGQKEAHAQAGVQVKQEPIESDEEEAEPPREVEPGQRQPSEQ

HDRP     566  GEQAAFMQQVIGKDLAPGFVIKVII-----------------------------------
HDAC9a   566  GEQAAFMQQPFLEPTHTRALSVRQAPLAAVGMDGLEKHRLVSRTHSSPAASVLPHPAMDR
HDAC9    566  GEQAAFMQQPFLEPTHTRALSVRQAPLAAVGMDGLEKHRLVSRTHSSPAASVLPHPAMDR
HDAC4    587  ELLFRQQALLLEQQRIHQLRNYQASMEAAGIPVSFGGHRPLSRAQSSPASATFPVSVQEP
```

FIG. 3B

```
HDRP           ------------------------------------------------------------
HDAC9a    626  PLQPGSATGIAYDPLMLKHQCVCGNSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKA
HDAC9     626  PLQPGSATGIAYDPLMLKHQCVCGNSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKA
HDAC4     647  PTKPRFTTGLVYDTLMLKHQCTCGSSSSHPEHAGRIQSIWSRLQETGLRGKCECIRGRKA

HDRP           ------------------------------------------------------------
HDAC9a    686  SLEEIQLVHSEHHSLLYGTNPLDGQKLDPRILLGDDSQKFFSSLPCGGLGVDSDTIWNEL
HDAC9     686  SLEEIQLVHSEHHSLLYGTNPLDGQKLDPRILLGDDSQKFFSSLPCGGLGVDSDTIWNEL
HDAC4     707  TLEELQTVHSEAHTLLYGTNPLNRQKLDSKKLLGSLASVFVR-LPCGGVGVDSDTIWNEV

HDRP           ------------------------------------------------------------
HDAC9a    746  HSSGAARMAVGCVIELASKVASGELKNGFAVVRPPGHHAEESTAMGFCFFNSVAITAKYL
HDAC9     746  HSSGAARMAVGCVIELASKVASGELKNGFAVVRPPGHHAEESTAMGFCFFNSVAITAKYL
HDAC4     766  HSAGAARLAVGCVVELVFKVATGELKNGFAVVRPPGHHAEESTPMGFCYFNSVAVAAKLL

HDRP           ------------------------------------------------------------
HDAC9a    806  RDQLNISKILIVDLDVHHGNGTQQAFYADPSILYISLHRYDEGNFFPGSGAPNEV RFISL
HDAC9     806  RDQLNISKILIVDLDVHHGNGTQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVGTGLG
HDAC4     826  QQRLSVSKILIVDWDVHHGNGTQQAFYSDPSVLYMSLHRYDDGNFFPGSGAPDEVGTGPG

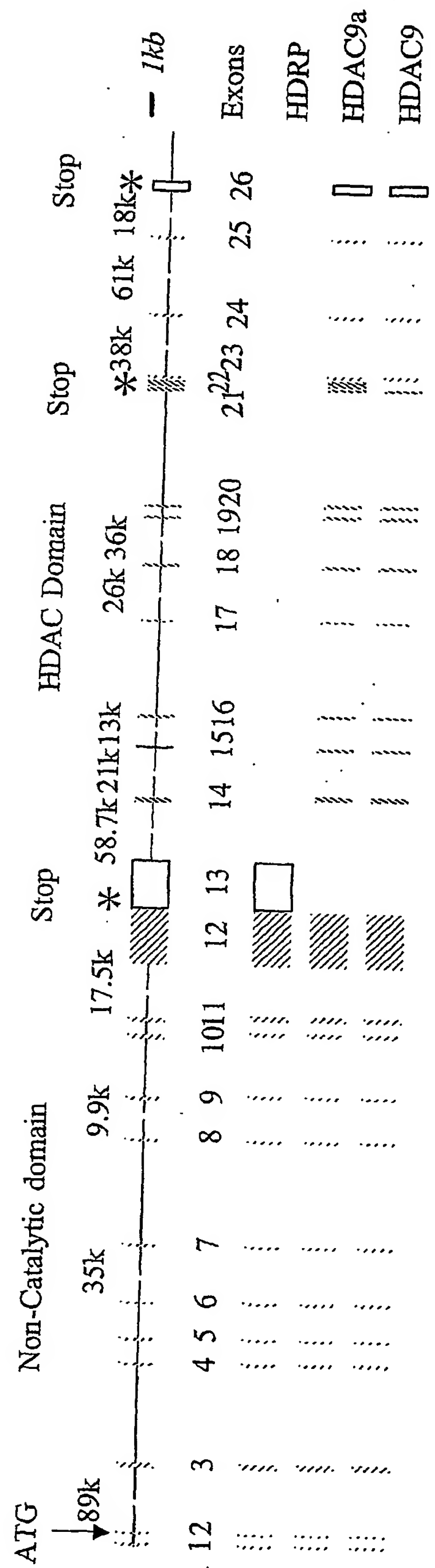
HDRP           ------------------------------------------------------------
HDAC9a    866  EPHFYLYLSGNCTA----------------------------------------------
HDAC9     866  ECYNINIAWTGGLDPPMGDVEYLEAFRTIVKPVAKEFDPDMVLVSAGFDALEGHTPLGG
HDAC4     886  VGFNVNMAFTGGLDPPMGDAEYLAAFRTVVMPIASEFAPDVVLVSSGFDAVEGHPTPLGG

HDRP           ------------------------------------------------------------
HDAC9a         ------------------------------------------------------------
HDAC9     926  YKVTAKCFGHLTKQLMTLADGRVVLALEGGHDLTAICDASEACVNALLGNELEPLAEDIL
HDAC4     946  YNLSARCFGYLTKQLMGLAGGRIVLALEGGHDLTAICDASEACVSALLGNELDPLPEKVL

HDRP           ------------------------------------------------------------
HDAC9a         ------------------------------------------------------------
HDAC9     986  HQSPNMNAVISLQKIIEIQSMSLKFS----------------------------------
HDAC4    1006  QQRPNANAVRSMEKVMEIHSKYWRCLQRTTSTAGRSLIEAQTCENEEAETVTAMASLSVG

HDRP           -------------------
HDAC9a         -------------------
HDAC9          -------------------
HDAC4    1066  VKPAEKRPDEEPMEEEPPL
```

FIG. 3C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35k
9.9k
17.5k
Stop
58.7k 21k 13k
HDAC Domain
26k 36k
Stop
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61k
18k
Stop
1kb
1 2
3
4 5 6
7
8 9
10 11
12
13
14
15 16
17
18
19 20
21 22 23
24
25
26
Exons
HDRP
HDAC9a
HDAC9

FIG. 4

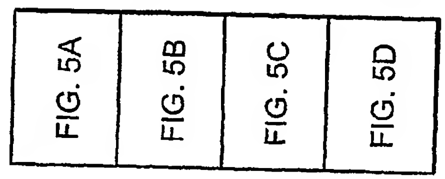


FIG. 5A
FIG. 5B
FIG. 5C
FIG. 5D

FIG. 5

1 /[1]ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca cttgcaggac tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact

101 ctaagccag/[2]a tggggtggct ggacgagagc agctcttggc tcagcaaaga **ATGCACAGTA** TGATCAGCTC AGT/[3]GGATGTG AAGTCAGAAG TTCCTGTGGG

201 CCTGGAGCCC ATCTCACCTT TAGACCTAAG GACAGACCTC AGGATGATGA TGCCCGTGGT GGACCCTGTT GTCCGTGAGA AGCAATTGCA GCAGGAATTA

301 CTTCTTATCC AGCAGCAGCA ACAAATCCAG AAGCAGCTTC TGATAGCAGA GTTTCAGAAA CAGCATGAGA ACTTGACACG GCAGCACCAG GCTCAGCTTC

401 AGGAGCATAT CAAG/[4]GAACTT CTAGCCATAA AACAGCAACA AGAACTCCTA GAAAAGGAGC AGAAACTGGA GCAGCAGAGG CAAGAACAGG AAGTAGAGAG

501 GCATCGCAGA GAACAGCAGC TTCCTCCTCT CAGAGGCAAA GATAGAGGAC GAGAAAG /[5]GGC AGTGGCAAGT ACAGAAGTAA AGCAGAAGCT TCAAGAGTTC

601 CTACTGAGTA AATCAGCAAC GAAAGACACT CCAACTAATG GAAAAAATCA TTCCGTGAGC CGCCATCCCA AGCTCTGGTA CACG/[6]GCTGCC CACCACACAT

701 CATTGGATCA AAGCTCTCCA CCCCTTAGTG GAACATCTCC ATCCTACAAG TACACATTAC CAGGAGCACA AGATGCAAAG GATGATTTCC CCCTTCGAAA

FIG. 5A

801 AACT/[7]GCCTCT GAGCCCAACT TGAAGGTGCG GTCCAGGTTA AAACAGAAAG TGGCAGAGAG GAGAAGCAGC CCCTTACTCA GGCGGAAGGA TGGAAATGTT

901 GTCACTTCAT TCAAGAAGCG AATGTTTGAG GTGACAG/[8]AAT CCTCAGTCAG TAGCAGTTCT CCAGGCTCTG GTCCCAGTTC ACCAAACAAT GGGCCAACTG

1001 GAAGTGTTAC TGAAAATGAG ACTTCGGTTT TGCCCCCTAC CCCTCATGCC GAG /[9]CAAATGG TTTCACAGCA ACGCATTCTA ATTCATGAAG ATTCCATGAA

1101 CCTGCTAAGT CTTTATACCT CTCCTTCTTT GCCCAACATT ACCTTGGGGC TTCCCGCAGT GCCATCCCAG CTCAATG /[10]CTT CGAATTCACT CAAAGAAAAG

1201 CAGAAGTGTG AGACGCAGAC GCTTAGGCAA GGTGTTCCTC TGCCTGGGCA GTATGGAGGC AGCATCCCGG CATCTTCCAG CCACCCTCAT GTTACTTTAG

1301 AGGGAAAGCC ACCCAACAGC AGCCACCAGG CTCTCCTGCA GCATTTATTA TTGAAAGAAC AAATGCGACA GCAAAAGCTT CTTGTAGCTG/[11] GTGGAGTTCC

1401 CTTACATCCT CAGTCTCCCT TGGCAACAAA AGAGAGAATT TCACCTGGCA TTAGAGGTAC CCACAAATTG CCCCGTCACA GACCCCTGAA CCGAACCCAG

1501 TCTGCACCTT TGCCTCAGAG CACGTTGGCT CAGCTGGTCA TTCAACAGCA ACACCAGCAA TTCTTGGAGA AGCAGAAGCA ATACCAGCAG CAGATCCACA

1601 TGAACAAA/[12]CT GCTTTCGAAA TCTATTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGGA AGAGCTTCAG GGGGACCAGG CGATGCAGGA

FIG. 5B

1701 AGACAGAGCG CCCTCTAGTG GCAACAGCAC TAGGAGCGAC AGCAGTGCTT GTGTGGATGA CACACTGGGA CAAGTTGGGG CTGTGAAGGT CAAGGAGGAA

1801 CCAGTGGACA GTGATGAAGA TGCTCAGATC CAGGAAATGG AATCTGGGGA GCAGGCTGCT TTTATGCAAC AG /[13]<u>GTAATAGG CAAAGATTTA GCTCCAGGAT TTGTAATTAA AGTCATTATC **TGA**</u>...... /[14]CCTTTCCT GGAACCCACG CACACACGTG

1901 CGCTCTCTGT GCGCCAAGCT CCGCTGGCTG CGGTTGGCAT GGATGGATTA GAGAAACACC GTCTCGTCTC CAGGACTCAC TCTTCCCCTG CTGCCTCTGT

2001 TTTACCTCAC CCAGCAATGG ACCGCCCCCT CCAGCCTGGC TCTGCAACTG /[15]GAATTGCCTA TGACCCCTTG ATGCTGAAAC ACCAGTGCGT TTGTGGCAAT

2101 TCCACCACCC ACCCTGAGCA TGCTGGACGA ATACAGAGTA TCTGGTCACG ACTGCAAGAA ACTGGGCTGC TAAATAAATG TGAG/[16]CGAATT CAAGGTCGAA

2201 AAGCCAGCCT GGAGGAAATA CAGCTTGTTC ATTCTGAACA TCACTCACTG TTGTATGGCA CCAACCCCCT GGACGGACAG AAGCTGGACC CCAGGATACT

2301 CCTAG/[17]GTGAT GACTCTCAAA AGTTTTTTTC CTCATTACCT TGTGGTGGAC TTGGG/[18]GTGGA CAGTGACACC ATTTGGAATG AGCTACACTC GTCCGGTGCT

2401 GCACGCATGG CTGTTGGCTG TGTCATCGAG CTGGCTTCCA AAGTGGCCTC AGGAGAGCTG AAGA /[19]ATGGGT TTGCTGTTGT GAGGCCCCCT GGCCATCACG

2501 CTGAAGAATC CACAGCCATG /[20]GGGTTCTGCT TTTTTAATTC AGTTGCAATT ACCGCCAAAT ACTTGAGAGA CCAACTAAAT ATAAGCAAGA TATTGATTGT

FIG. 5C

2601 AGATCTG/[21]GAT GTTCACCATG GAAACGGTAC CCAGCAGGCC TTTTATGCTG ACCCCAGCAT CCTGTACATT TCACTCCATC GCTATGATGA AGGGAACTTT

2701 TTCCCTGGCA GTGGAGCCCC AAATGAGG/[22]TT CGGTTTATTT CTTTAGAGCC CCACTTTTAT TTGTATCTTT CAGGTAATTG **CATTGCATGA** ttacccctaa

2801 ttttcttgtc ctttgctggt gttttaaatt acacgagatt actgaattgt cccatgggac caagaaccag tgcagaacaa gtgcataacc cagagcactg

2901 tttgtcaggg aaggttgggc tgatttgatg tgttgtttga tgtttatttc aagagctccc atgtgcttgt tttcctctct tcttgctttc ttccatttgc

3001 tctcttctct gcccaccgtg gtgtgtcttt ctcttcccag /[23]gttggaacag gccttggaga agggtacaat ataaatattg cctggacagg tggccttgat

3101 cctcccatgg gagatgttga gtaccttgaa gcattcag/[24]ga ccatcgtgaa gcctgtggcc aaagagtttg atccagacat ggtcttagta tctgctggat

3201 ttgatgcatt ggaaggccac acccctcctc taggagggta caaagtgacg gcaaaatg/[25]tt ttggtcattt gacgaagcaa ttgatgacat tggctgatgg

3301 acgtgtggtg ttggctctag aaggaggaca tgatctcaca gccatctgtg atgcatcaga agcctgtgta aatgcccttc taggaaatga g/[26]ctggagcca

3401 cttgcagaag atattctcca ccaaagcccg aatatgaatg ctgttatttc tttacagaag atcattgaaa ttcaaagtat gtctttaaag ttctct**taa**.....

FIG. 5D

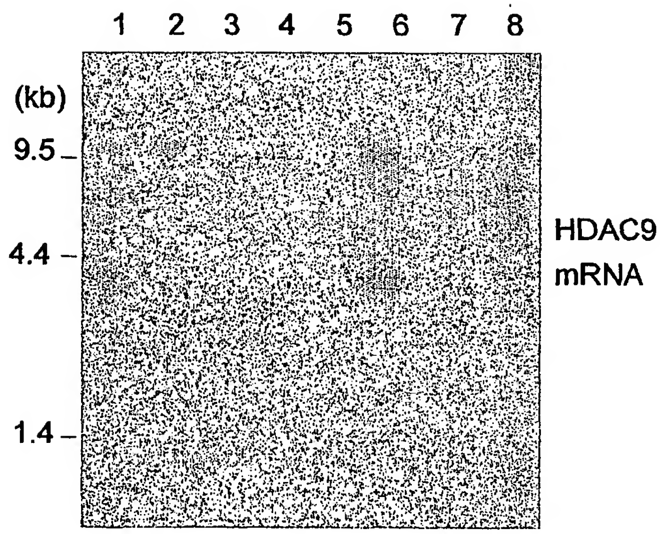


FIG. 6A

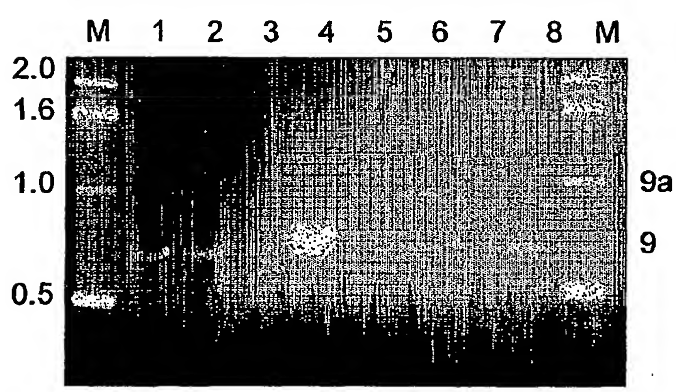
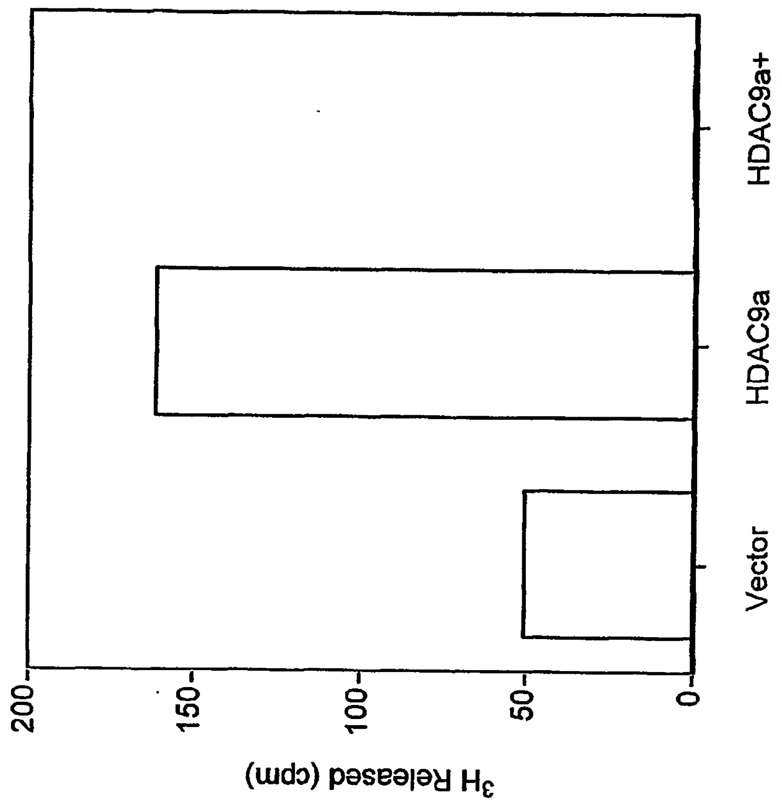
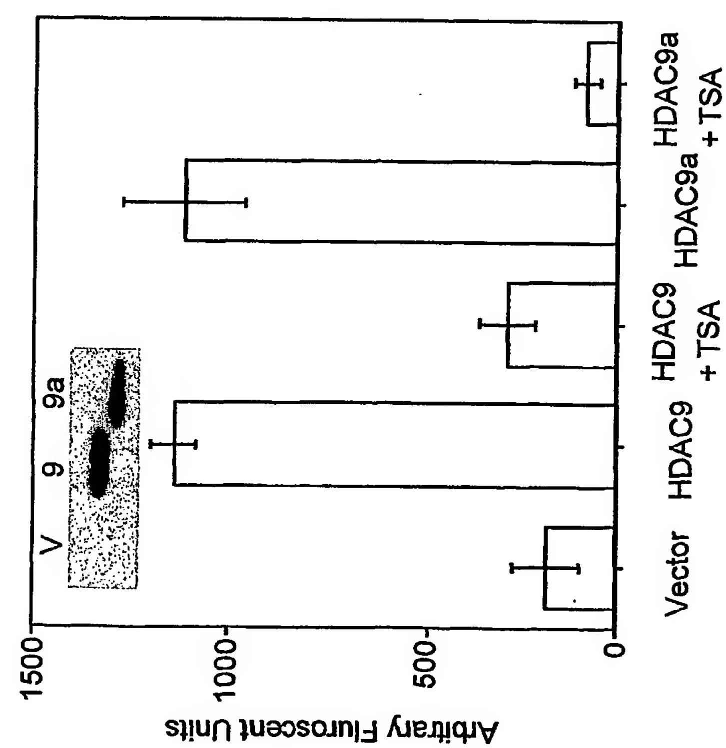


FIG. 6B



3H Released (cpm)
200
150
100
50
0
Vector
HDAC9a
HDAC9a+

FIG. 8



Arbitrary Fluroscent Units
1500
1000
500
0
V
9
9a
Vector
HDAC9
HDAC9 +TSA
HDAC9a
HDAC9a +TSA

FIG. 7

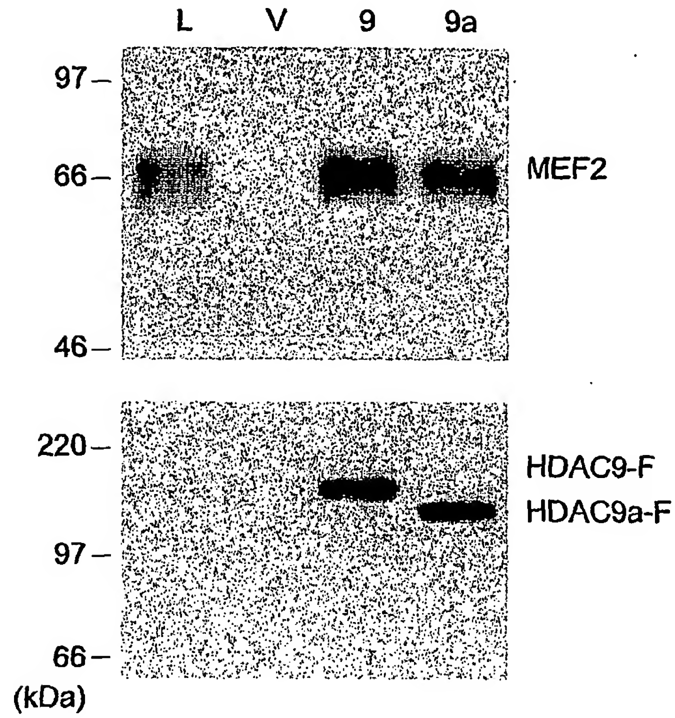

L
V
9
9a
97
66
46
MEF2
220
97
66
HDAC9-F
HDAC9a-F
(kDa)

FIG. 9A

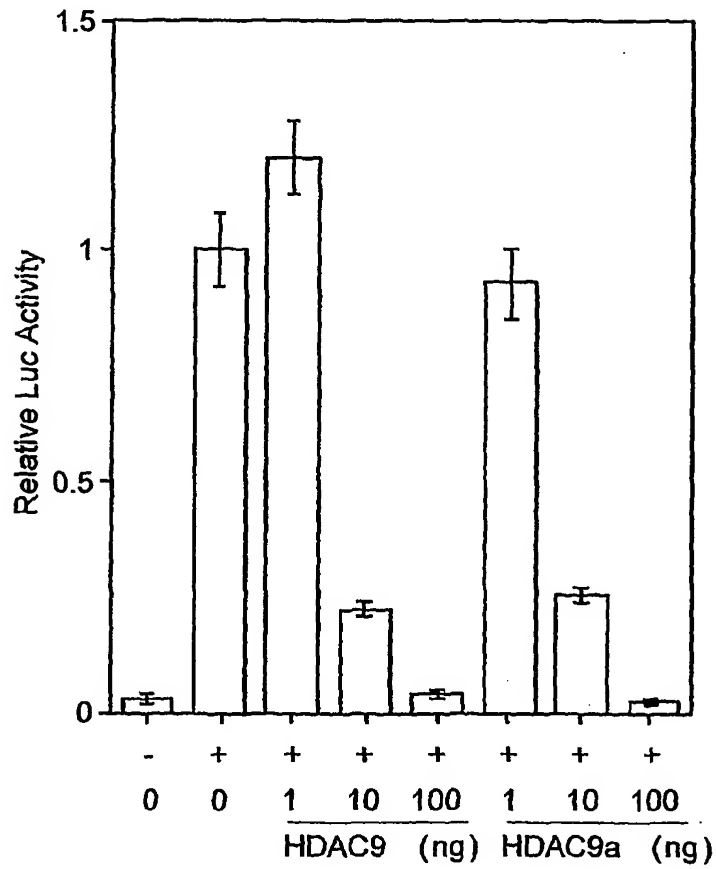

1.5
1
0.5
0
Relative Luc Activity
-
+
+
+
+
+
+
+
0
0
1
10
100
1
10
100
HDAC9
(ng)
HDAC9a
(ng)

FIG. 9B

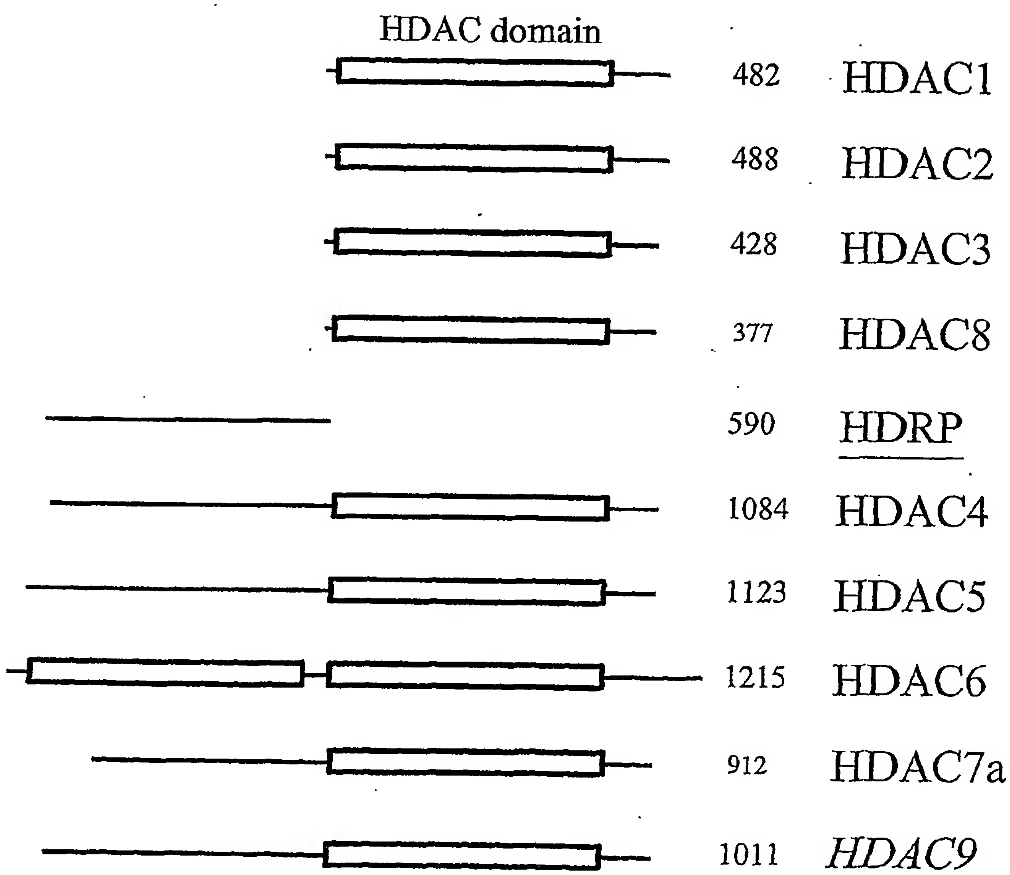

HDAC domain
482 HDAC1
488 HDAC2
428 HDAC3
377 HDAC8
590 HDRP
1084 HDAC4
1123 HDAC5
1215 HDAC6
912 HDAC7a
1011 HDAC9

FIG. 10

FIG. 11A
FIG. 11B
FIG. 11C
FIG. 11D
FIG. 11E
FIG. 11F

FIG. 11

FIG. 11A

cccattcgccattcaggctgcgcaactgttgggaagggcgatcggtgcgggcctcttcgctattacgccagctggcgaaaggg
ggatgtgctgcaaggcgattaagttgggtaacgcccagggttttcccagtcacgacgttgtaaaacgacggccagtgccaagct
gatctaatcaatattggccattagccatattattcattggttatatagcataaatcaatattggctattggccattgcatacgttgtatcca
tatcataatatgtacatttatattggctcatgtccaacattaccgccatgttgacattgattattgactagttattaatagtaatcaattacg
gggtcattagttcatagcccatatatggagttccgcgttacataacttacggtaaatggcccgcctggcgaccgcccagcgaccc
ccgcccgttgacgtcaatagtgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacg

gtaaactgcccacttggcagtacatcaagtgtatcatatgccaagtccgccccctattgacgtcaatgacggtaaatggcccgcct
agcattatgcccagtacatgaccttacgggagtttcctacttggcagtacatctacgtattagtcatcgctattaccatggtgatgcg
gttttggcagtacaccaatgggcgtggatagcggtttgactcacggggatttccaagtctccaccccattgacgtcaatgggagtt
tgttttggcaccaaaatcaacgggactttccaaaatgtcgtaataaccccgccccgttgacgcaaatgggcggtaggcgtgtacg
gtgggaggtctatataagcagagctcgtttagtgaaccgtcagaattcaagcttgcggccgcagatctatcgatctgcaggatatc
(EcoRV)
acc

ATGCACAGTATGATCAGCTCAGTGGATGTGAAGTCAGAAGTTCCTGTGGG
CCTGGAGCCCATCTCACCTTTAGACCTAAGGACAGACCTCAGGATGATGA
TGCCCGTGGTGGACCCTGTTGTCCGTGAGAAGCAATTGCAGCAGGAATTA
CTTCTTATCCAGCAGCAGCAACAAATCCAGAAGCAGCTTCTGATAGCAGA
GTTTCAGAAACAGCATGAGAACTTGACACGGCAGCACCAGGCTCAGCTTC
AGGAGCATATCAAGGAACTTCTAGCCATAAAACAGCAACAAGAACTCCTA
GAAAAGGAGCAGAAACTGGAGCAGCAGAGGCAAGAACAGGAAGTAGAGAG
GCATCGCAGAGAACAGCAGCTTCCTCCTCTCAGAGGCAAAGATAGAGGAC
GAGAAAGGGCAGTGGCAAGTACAGAAGTAAAGCAGAAGCTTCAAGAGTTC
CTACTGAGTAAATCAGCAACGAAAGACACTCCAACTAATGGAAAAAATCA
TTCCGTGAGCCGCCATCCCAAGCTCTGGTACACGGCTGCCCACCACACAT
CATTGGATCAAAGCTCTCCACCCCTTAGTGGAACATCTCCATCCTACAAG

FIG. 11B

TACACATTACCAGGAGCACAAGATGCAAAGGATGATTTCCCCCTTCGAAA
AACTGCCTCTGAGCCCAACTTGAAGGTGCGGTCCAGGTTAAAACAGAAAG
TGGCAGAGAGGAGAAGCAGCCCCTTACTCAGGCGGAAGGATGGAAATGTT
GTCACTTCATTCAAGAAGCGAATGTTTGAGGTGACAGAATCCTCAGTCAG
TAGCAGTTCTCCAGGCTCTGGTCCCAGTTCACCAAACAATGGCCAACTG
GAAGTGTTACTGAAAATGAGACTTCGGTTTTGCCCCCTACCCCTCATGCC
GAGCAAATGGTTTCACAGCAACGCATTCTAATTCATGAAGATTCCATGAA
CCTGCTAAGTCTTTATACCTCTCCTTCTTTGCCCAACATTACCTTGGGGC
TTCCCGCAGTGCCATCCCAGCTCAATGCTTCGAATTCACTCAAAGAAAAG
CAGAAGTGTGAGACGCAGACGCTTAGGCAAGGTGTTCCTCTGCCTGGGCA
GTATGGAGGCAGCATCCCGGCATCTTCCAGCCACCCTCATGTTACTTTAG
AGGGAAAGCCACCCAACAGCAGCCACCAGGCTCTCCTGCAGCATTTATTA
TTGAAAGAACAAATGCGACAGCAAAAGCTTCTTGTAGCTGGTGGAGTTCC
CTTACATCCTCAGTCTCCCTTGGCAACAAAAGAGAGAATTTCACCTGGCA
TTAGAGGTACCCACAAATTGCCCCGTCACAGACCCCTGAACCGAACCCAG
TCTGCACCTTTGCCTCAGAGCACGTTGGCTCAGCTGGTCATTCAACAGCA
ACACCAGCAATTCTTGGAGAAGCAGAAGCAATACCAGCAGCAGATCCACA
TGAACAAACTGCTTTCGAAATCTATTGAACAACTGAAGCAACCAGGCAGT
CACCTTGAGGAAGCAGAGGAAGAGCTTCAGGGGGACCAGGCGATGCAGGA
AGACAGAGCGCCCTCTAGTGGCAACAGCACTAGGAGCGACAGCAGTGCTT
GTGTGGATGACACACTGGGACAAGTTGGGGCTGTGAAGGTCAAGGAGGAA
CCAGTGGACAGTGATGAAGATGCTCAGATCCAGGAAATGGAATCTGGGGA
GCAGGCTGCTTTTATGCAACAGCCTTTCCTGGAACCCACGCACACACGTG
CGCTCTCTGTGCGCCAAGCTCCGCTGGCTGCGGTTGGCATGGATGGATTA

FIG. 11C

GAGAAACACCGTCTCGTCTCCAGGACTCACTCTTCCCCTGCTGCCTCTGT
TTTACCTCACCCAGCAATGGACCGCCCCCTCCAGCCTGGCTCTGCAACTG
GAATTGCCTATGACCCCTTGATGCTGAAACACCAGTGCGTTTGTGGCAAT
TCCACCACCCACCCTGAGCATGCTGGACGAATACAGAGTATCTGGTCACG
ACTGCAAGAAACTGGGCTGCTAAATAAATGTGAGCGAATTCAAGGTCGAA
AAGCCAGCCTGGAGGAAATACAGCTTGTTCATTCTGAACATCACTCACTG
TTGTATGGCACCAACCCCCTGGACGGACAGAAGCTGGACCCCAGGATACT
CCTAGGTGATGACTCTCAAAAGTTTTTTTCCTCATTACCTTGTGGTGGAC
TTGGGGTGGACAGTGACACCATTTGGAATGAGCTACACTCGTCCGGTGCT
GCACGCATGGCTGTTGGCTGTGTCATCGAGCTGGCTTCCAAAGTGGCCTC
AGGAGAGCTGAAGAATGGGTTTGCTGTTGTGAGGCCCCCTGGCCATCACG
CTGAAGAATCCACAGCCATGGGGTTCTGCTTTTTTAATTCAGTTGCAATT
ACCGCCAAATACTTGAGAGACCAACTAAATATAAGCAAGATATTGATTGT
AGATCTGGATGTTCACCATGGAAACGGTACCCAGCAGGCCTTTTATGCTG
ACCCCAGCATCCTGTACATTTCACTCCATCGCTATGATGAAGGGAACTTT
TTCCCTGGCAGTGGAGCCCCAAATGAGGTTGGAACAGGCCTTGGAGAAGG
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GCTCTAGAAGGAGGACATGATCTCACAGCCATCTGTGATGCATCAGAAGC
CTGTGTAAATGCCCTTCTAGGAAATGAGCTGGAGCCACTTGCAGAAGATA
TTCTCCACCAAAGCCCGAATATGAATGCTGTTATTTCTTTACAGAAGATC
ATTGAAATTCAAAGTATGTCTTTAAAGTTCTCT

FIG. 11D

(BamHI)ggatccggtaccagattacaaggacgacgatgacaagtagatcccgggtggcatccctgtgacccctccccagtg
cctctcctggccttggaagttgccactccagtgcccaccagccttgtcctaataaaattaagttgcatcattttgtctgactaggtgtc
ctctataatattatggggtggaggggggtggtatggagcaaggggcccaagttgggaagacaacctgtagggcctgcggggtc
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gccaggctggtctccaactcctaatctcaggtgatctacccaccttggcctcccaaattgctgggattacaggcgtgaaccactgc
tcccttccctgtccttctgattttaaaataactataccagcaggaggacgtccagacacagcataggctacctgccatggcccaac
cggtgggacatttgagttgcttgcttggcactgtcctctcatgcgttgggtccactcagtagatgcctgttgaattgggtacgcggc
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accatagtcccgcccctaactccgcccatcccgcccctaactccgcccagttccgcccattctccgccccatggctgactaatttt
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ctgtgtgaaattgttatccgctcacaattccacacaacatacgagccggaagcataaagtgtaaagcctggggtgcctaatgagt
gagctaactcacattaattgcgttgcgctcactgcccgctttccagtcgggaaacctgtcgtgccagctgcattaatgaatcggcc
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gcgagcggtatcagctcactcaaaggcggtaatacggttatccacagaatcaggggataacgcaggaaagaacatgtgagca
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tgcgctctcctgttccgaccctgccgcttaccggatacctgtccgcctttctcccttcgggaagcgtggcgctttctcaatgctcac

FIG. 11E

gctgtaggtatctcagttcggtgtaggtcgttcgctccaagctgggctgtgtgcacgaaccccccgttcagcccgaccgctgcgc
cttatccggtaactatcgtcttgagtccaacccggtaagacacgacttatcgccactggcagcagccactggtaacaggattagc
agagcgaggtatgtaggcggtgctacagagttcttgaagtggtggcctaactacggctacactagaagaacagtatttggtatct
gcgctctgctgaagccagttaccttcggaaaaagagttggtagctcttgatccggcaaacaaaccaccgctggtagcggtggttt
ttttgtttgcaagcagcagattacgcgcagaaaaaaaggatctcaagaagatcctttgatcttttctacggggtctgacgctcagtg
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aattt

FIG. 11F

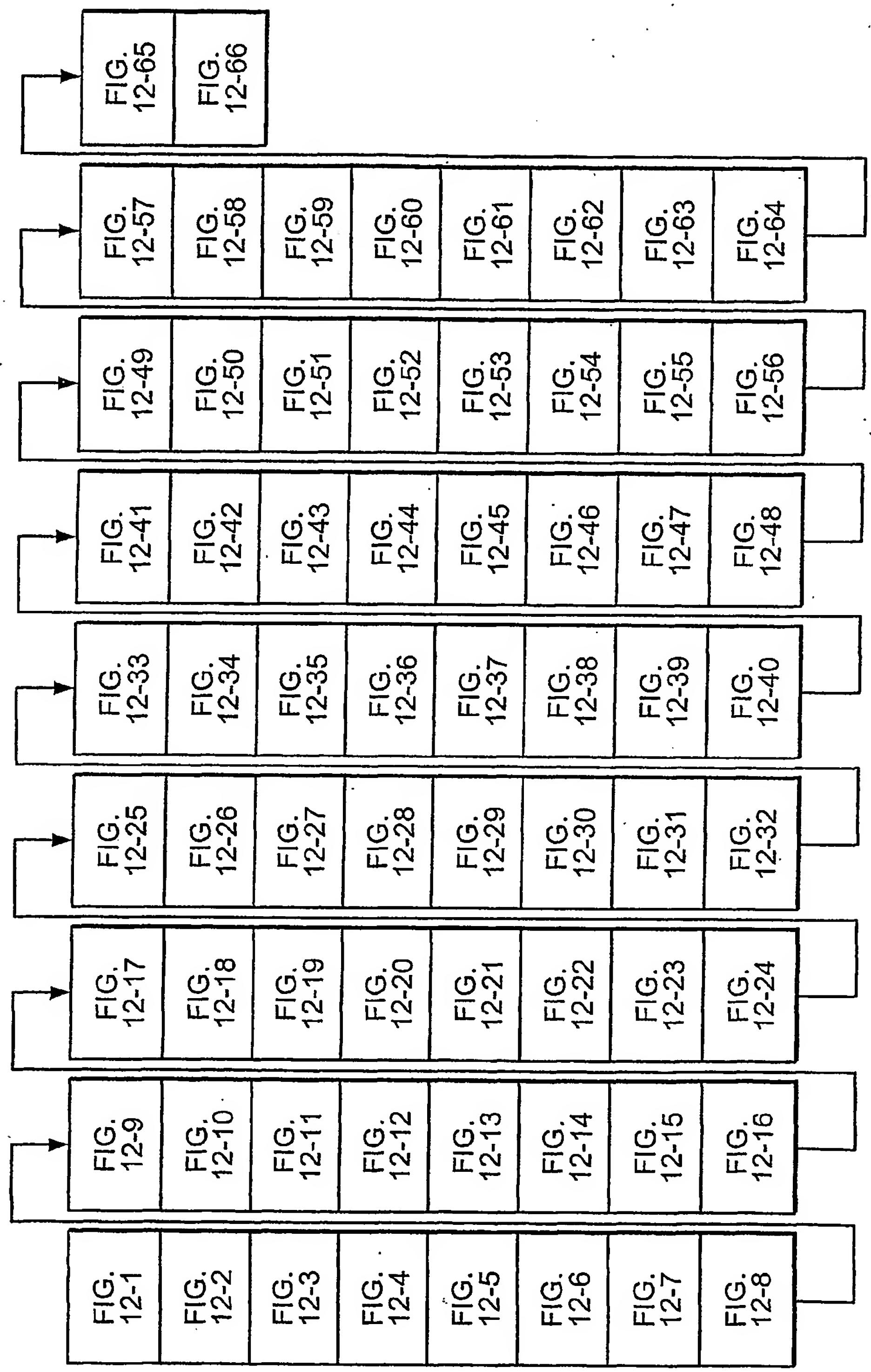
FIG. 12-1
FIG. 12-2
FIG. 12-3
FIG. 12-4
FIG. 12-5
FIG. 12-6
FIG. 12-7
FIG. 12-8
FIG. 12-9
FIG. 12-10
FIG. 12-11
FIG. 12-12
FIG. 12-13
FIG. 12-14
FIG. 12-15
FIG. 12-16
FIG. 12-17
FIG. 12-18
FIG. 12-19
FIG. 12-20
FIG. 12-21
FIG. 12-22
FIG. 12-23
FIG. 12-24
FIG. 12-25
FIG. 12-26
FIG. 12-27
FIG. 12-28
FIG. 12-29
FIG. 12-30
FIG. 12-31
FIG. 12-32
FIG. 12-33
FIG. 12-34
FIG. 12-35
FIG. 12-36
FIG. 12-37
FIG. 12-38
FIG. 12-39
FIG. 12-40
FIG. 12-41
FIG. 12-42
FIG. 12-43
FIG. 12-44
FIG. 12-45
FIG. 12-46
FIG. 12-47
FIG. 12-48
FIG. 12-49
FIG. 12-50
FIG. 12-51
FIG. 12-52
FIG. 12-53
FIG. 12-54
FIG. 12-55
FIG. 12-56
FIG. 12-57
FIG. 12-58
FIG. 12-59
FIG. 12-60
FIG. 12-61
FIG. 12-62
FIG. 12-63
FIG. 12-64
FIG. 12-65
FIG. 12-66

FIG. 12

pFLAG-CMV-5b-HDAC9

7699 base pairs

Graphic map | Table by enzyme name

```
                                          BstMCI
                  AviII                   PvuI BsiEI       EarI          MspA1I
            BglI  FspI                    BsaOI            Eam1104I      PvuII
cccattcgccattcaggctgcgcaactgttgggaagggcgatcggtgcgggcctcttcgctattacgccagctgg
base pairs
gggtaagcggtaagtccgacgcgttgacaacccttcccgctagccacgcccggagaagcgataatgcggtcgacc
1 to 75
                  Acc16I                  BspCI            Ksp632I     NspBII
                                          Bsh1285I
                                          Ple19I

cgaaagggggatgtgctgcaaggcgattaagttgggtaacgcccagggttttcccagtcacgacgttgtaaaacg
base pairs
gctttccccctacacgacgttccgctaattcaacccattgcgggtcccaaaagggtcagtgctgcaacattttgc
76 to 150
```

FIG. 12-1

```
                                       MscI
                                     CfrI
  EaeI                            SspI MluNI
acggccagtgccaagctgatctaatcaatattggccattagccatattattcattggttatatagcataaatcaa
base pairs
tgccggtcacggttcgactagattagttataaccggtaatcggtataataagtaaccaatatatcgtatttagtt
151 to 225
  CfrI                               EaeI
                                       BalI

             MscI
             MluNI                                    SspBI
 SspI       EaeI      BsrDI                          Bsp1407I
tattggctattggccattgcatacgttgtatccatatcataatatgtacatttatattggctcatgtccaacatt
base pairs
ataaccgataaccggtaacgtatgcaacataggtatagtattatacatgtaaatataaccgagtacaggttgtaa
226 to 300
           CfrI                                       BsrGI
             BalI
```

FIG. 12-2

```
                                                VspI
                       HincII          SpeI     PshBI
accgccatgttgacattgattattgactagttattaatagtaatcaattacggggtcattagttcatagcccata
base pairs
tggcggtacaactgtaactaataactgatcaataattatcattagttaatgccccagtaatcaagtatcgggtat
301 to 375
                       HindII          AclNI    AsnI
                                                AseI

                                                                           HinlI
                                                     BstMCI                 AcyI
                                              BglI   BsaOI                HincII
tatggagttccgcgttacataacttacggtaaatggcccgcctggcgaccgcccagcgacccccgcccgttgacg
base pairs
atacctcaaggcgcaatgtattgaatgccatttaccgggcggaccgctggcgggtcgctgggggcgggcaactgc
376 to 450
                                                     Bsh1285I             HindII
                                                     BsiEI
```

FIG. 12-3

```
                                                                   BbiII
  AatII                                                           Hin1I
  BbiII                                                            AcyI AatII
tcaatagtgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacgg
base pairs
agttatcactgcatacaagggtatcattgcggttatccctgaaaggtaactgcagttacccacctcataaatgcc
451 to 525
  Hsp92I                                                          Msp17I
                                                                   BsaHI
                                                                  Hsp92I

                                                                           BbiII
                                                                          Hin1I
           BglI                      NdeI                                  AcyI AatII
taaactgcccacttggcagtacatcaagtgtatcatatgccaagtccgccccctattgacgtcaatgacggtaaa
base pairs
atttgacgggtgaaccgtcatgtagttcacatagtatacggttcaggcgggggataactgcagttactgccattt
526 to 600
                                     FauNDI                                Msp17I
                                                                            BsaHI
                                                                           Hsp92I
```

FIG. 12-4

```
                                                                       BstSNI
                                                                       SnaBI
tggcccgcctagcattatgcccagtacatgaccttacgggagtttcctacttggcagtacatctacgtattagtc
base pairs
accgggcggatcgtaatacgggtcatgtactggaatgccctcaaaggatgaaccgtcatgtagatgcataatcag
601 to 675

                                                                       BsaAI
                                                                      Eco105I

          NcoI Bsp19I
          StyI BstDSI
          EcoT14I
atcgctattaccatggtgatgcggttttggcagtacaccaatgggcgtggatagcggtttgactcacggggattt
base pairs
tagcgataatggtaccactacgccaaaaccgtcatgtggttacccgcacctatcgccaaactgagtgcccctaaa
676 to 750
          BssT1I
          ErhI Eco130I
          DsaI MslI
```

FIG. 12-5

```
              BbiII
              Hin1I                     AccB1I
              AcyI AatII                BshNI
ccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatgtcgt
base pairs
ggttcagaggtggggtaactgcagttaccctcaaacaaaaccgtggttttagttgccctgaaaggttttacagca
751 to 825
              Msp17I                    BanI
              BsaHI                     Eco64I
              Hsp92I

                                                                          BanII
                                                                         Eco24I
             HincII                                                     EcoICRI
aataaccccgccccgttgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcagagctcgttta
base pairs
ttattggggcggggcaactgcgtttacccgccatccgcacatgccaccctccagatatattcgtctcgagcaaat
826 to 900
             HindII                                                     Ecl136II
                                                                          SacI
```

FIG. 12-6

```
FriOI
SstI
BsiHKAI                    EagI XmaIII BstYI BspDI BcgI Eco32I
 Bbv12I      AcsI          CciNI Bsh1285I BstX2I BanIII PstI         BclI
AspHI        ApoI  HindIII BstZI BstMCI MflI Bsa29I SfcI             Ksp22I
gtgaaccgtcagaattcaagcttgcggccgcagatctatcgatctgcaggatatcaccatgcacagtatgatcag
base pairs
cacttggcagtcttaagttcgaacgccggcgtctagatagctagacgtcctatagtggtacgtgtcatactagtc
901 to 975
 Psp124BI    EcoRI         EaeI Eco52I BglII BscI BspXI BstSFI       FbaI
                           CfrI EclXI BsiEI BseCI Bsu15I EcoRV
Alw21I                     NotI BsaOI XhoII ClaI Bsp106I

                                           FriOI         CvnI      CvnI
                                          Eco24I         AocI      AocI
                                         BpmI            Bsu36I    Bsu36I
ctcagtggatgtgaagtcagaagttcctgtgggcctggagcccatctcacctttagacctaaggacagacctcag
base pairs
gagtcacctacacttcagtcttcaaggacacccggacctcgggtagagtggaaatctggattcctgtctggagtc
976 to 1050
                                         GsuI            Eco81I    Eco81I
                                           BanII         Bse21I    Bse21I
```

FIG. 12-7

```
         DsaI              DrdI                MfeI                 Asp700I
gatgatgatgcccgtggtggaccctgttgtccgtgagaagcaattgcagcaggaattacttcttatccagcagca
base pairs
ctactactacgggcaccacctgggacaacaggcactcttcgttaacgtcgtccttaatgaagaataggtcgtcgt
1051 to 1125
         BstDSI                                MunI                 XmnI
```

FIG. 12-8

```
                        AlwNI
gcaacaaatccagaagcagcttctgatagcagagtttcagaaacagcatgagaacttgacacggcagcaccaggc
base pairs
cgttgtttaggtcttcgtcgaagactatcgtctcaaagtctttgtcgtactcttgaactgtgccgtcgtggtccg
1126 to 1200

BlpI
CelII     Eco57I
                                                                  EcoNI
                                                                            AlwNI
tcagcttcaggagcatatcaaggaacttctagccataaaacagcaacaagaactcctagaaaggagcagaaact
base pairs
agtcgaagtcctcgtatagttccttgaagatcggtattttgtcgttgttcttgaggatctttcctcgtctttga
1201 to 1275
Bsp1720I
Bpu1102I
```

FIG. 12-9

```
    BpmI                                                          BseRI
ggagcagcagaggcaagaacaggaagtagagaggcatcgcagagaacagcagcttcctcctctcagaggcaaaga
base pairs
cctcgtcgtctccgttcttgtccttcatctctccgtagcgtctcttgtcgtcgaaggaggagagtctccgtttct
1276 to 1350
    GsuI                                                           EcoNI

                                           HindIII
tagaggacgagaaagggcagtggcaagtacagaagtaaagcag aagcttcaagagttcctactgagtaaatcagc
base pairs
atctcctgctctttcccgtcaccgttcatgtcttcatttcgtc ttcgaagttctcaaggatgactcatttagtcg
1351 to 1425
```

FIG. 12-10

```
                    Van91I                                 Van91I
                    AccB7I                                 AccB7I
aacgaaagacactccaactaatggaaaaatcattccgtgagccgccatcccaagctctggtacacggctgccca
base pairs
ttgctttctgtgaggttgattacctttttagtaaggcactcggcggtagggttcgagaccatgtgccgacgggt
1426 to 1500
                    Esp1396I                               Esp1396I
                    PflMI                                  PflMI
```

```
ccacacatcattggatcaaagctctccaccccttagtggaacatctccatcctacaagtacacattaccaggagc
base pairs
ggtgtgtagtaacctagtttcgagaggtggggaatcaccttgtagaggtaggatgttcatgtgtaatggtcctcg
1501 to 1575
```

FIG. 12-11

```
                         BstBI
 Alw21I                  Bpu14I            FriOI
 AspHI                   Csp45I            Eco24I
acaagatgcaaaggatgatttccccttcgaaaaactgcctctgagcccaacttgaaggtgcggtccaggttaaa
base pairs
tgttctacgtttcctactaaaggggaagcttttgacggagactcgggttgaacttccacgccaggtccaattt
1576 to 1650
 BsiHKAI                  SfuI Bsp119I      BanII
 Bbv12I                   NspV
                          LspI


                     BseRI        EcoNI
acagaaagtggcagagaggagaagcagccccttactcaggcggaaggatggaaatgttgtcacttcattcaagaa
base pairs
tgtctttcaccgtctctcctcttcgtcggggaatgagtccgccttcctacctttacaacagtgaagtaagttctt
1651 to 1725
```

FIG. 12-12

```
                                        Van91I
                                        AccB7I                Van91I
                                      BpmI PflMI               AccB7I
gcgaatgtttgaggtgacagaatcctcagtcagtagcagttctccaggctctggtcccagttcaccaaacaatgg
base pairs
cgcttacaaactccactgtcttaggagtcagtcatcgtcaagaggtccgagaccagggtcaagtggtttgttacc
1726 to 1800
                                        GsuI                 Esp1396I
                                      Esp1396I                  PflMI
                                        AlwNI
```

```
gccaactggaagtgttactgaaaatgagacttcggttttgccccctacccctcatgccgagcaaatggtttcaca
base pairs
cggttgaccttcacaatgacttttactctgaagccaaaacgggggatggggagtacggctcgtttaccaaagtgt
1801 to 1875
```

FIG. 12-13

```
        BsaMI
        Mva1269I                  BspMI                       XcmI
gcaacgcattctaattcatgaagattccatgaacctgctaagtctttatacctctccttctttgcccaacattac
base pairs
cgttgcgtaagattaagtacttctaaggtacttggacgattcagaaatatggagaggaagaaacgggttgtaatg
1876 to 1950
        BsmI RcaI
             BspHI

                                  BstBI AcsI
ErhI                              Bpu14I
BssT1I                            Csp45I
                                                                Esp3I
cttggggcttcccgcagtgccatcccagctcaatgcttc gaattcactcaaagaaaagcagaagtgtgagacgca
base pairs
gaaccccgaagggcgtcacggtagggtcgagttacgaag cttaagtgagtttcttttcgtcttcacactctgcgt
1951 to 2025
EcoT14I                           SfuI Bsp119I
                                                                BsmBI
StyI                              NspV ApoI
Eco130I                           LspI EcoRI
```

FIG. 12-14

```
                                                                   MslI
gacgcttaggcaaggtgttcctctgcctgggcagtatggaggcagcatcccggcatcttccagccaccctcatgt
base pairs
ctgcgaatccgttccacaaggagacggacccgtcatacctccgtcgtagggccgtagaaggtcggtgggagtaca
2026 to 2100

                                             PstI
                                          SfcI
tactttagagggaaagccacccaacagcagccaccaggctctc ctgcagcatttattattgaaagaacaaatgcg
base pairs
atgaaatctccctttcggtgggttgtcgtcggtggtccgagag gacgtcgtaaataataactttcttgtttacgc
2101 to 2175
                                          BstSFI
```

FIG. 12-15

```
        HindIII                                            Eco130I
                                                            StyI
                                                            EcoT14I           ApoI
acagcaaaagcttcttgtagctggtggagttcccttacatcctcagtctcccttggcaacaaaagagagaatttc
base pairs
tgtcgttttcgaagaacatcgaccacctcaagggaatgtaggagtcagagggaaccgttgttttctctcttaaag
2176 to 2250
                                                            BssT1I            AcsI
                                                            ErhI

              Asp718I
              Acc65I
              BshNI                                                        BsgI
acctggcattagaggtacccacaaattgccccgtcacagacccctgaaccgaacccagtctgcacctttgcctca
base pairs
tggaccgtaatctccatgggtgtttaacggggcagtgtctggggacttggcttgggtcagacgtggaaacggagt
2251 to 2325
              BanI KpnI
              AccB1I
              Eco64I
```

FIG. 12-16

```
             Bpu1102I
     Alw21I  Bsp1720I
     AspHI   CelII
gagcacgttggctcagctggtcattcaacagcaacaccagcaattcttggagaagcagaagcaataccagcagca
base pairs
ctcgtgcaaccgagtcgaccagtaagttgtcgttgtggtcgttaagaacctcttcgtcttcgttatggtcgtcgt
2326 to 2400
     BsiHKAI     PvuII
     Bbv12I BlpI MspA1I
                 NspBII

                       BstBI
MflI                   Bpu14I
XhoII                  Csp45I                  Eco57I
gatccacatgaacaaactgctttcgaaatctattgaacaactgaagcaaccaggcagtcaccttgaggaagcaga
base pairs
ctaggtgtacttgtttgacgaaagctttagataacttgttgacttcgttggtccgtcagtggaactccttcgtct
2401 to 2475
BstYI                  SfuI Bsp119I
BstX2I                 NspV
                       LspI
```

FIG. 12-17

EarI
Eam1104I Bbv16II
Asp700I BbsI Bsp143II
ggaagagcttcaggggaccaggcgatgcaggaagacagagcgccctctagtggcaacagcactaggagcgacag
base pairs
ccttctcgaagtcccctggtccgctacgtccttctgtctcgcgggagatcaccgttgtcgtgatcctcgctgtc
2476 to 2550
XmnI Eco57I BpiI HaeII
Ksp632I BpuAI BstH2I
SapI

BcgI
cagtgcttgtgtggatgacacactgggacaagttggggctgtgaaggtcaaggaggaaccagtggacagtgatga
base pairs
gtcacgaacacacctactgtgtgaccctgttcaaccccgacacttccagttcctccttggtcacctgtcactact
2551 to 2625

FIG. 12-18

```
          MflI      Van91I
          XhoII     AccB7I
agatgctcagatccaggaaatggaatctggggagcaggctgcttttatgcaacagcctttcctggaacccacgca
base pairs
tctacgagtctaggtcctttaccttagacccctcgtccgacgaaaatacgttgtcggaaaggaccttgggtgcgt
2626 to 2700
          BstYI     Esp1396I
          BstX2I    PflMI


     PmaCI
     PmlI
  AflIII                               NspBII
                                                                         Esp3I
cacacgtgcgctctctgtgcgccaagctccgctggctgcggttggcatggatggattagagaaacaccgtctcgt
base pairs
gtgtgcacgcgagagacacgcggttcgaggcgaccgacgccaaccgtacctacctaatctctttgtggcagagca
2701 to 2775
   MslI Eco72I                         MspA1I
                                                                         BsmBI
     BsaAI
     BbrPI
```

FIG. 12-19

```
                EarI
     BpmI       Eam1104I                                      BsrDI          BpmI
ctccaggactcactcttcccctgctgcctctgttttacctcacccagcaatggaccgcccctccagcctggctc
base pairs
gaggtcctgagtgagaaggggacgacggagacaaaatggagtgggtcgttacctggcggggaggtcggaccgag
2776 to 2850
     GsuI       Ksp632I                                                      GsuI
```

```
                                                     XcmI
tgcaactggaattgcctatgaccccttgatgctgaaacaccagtgcgtttgtggcaattccaccacccaccctga
base pairs
acgttgaccttaacggatactggggaactacgactttgtggtcacgcaaacaccgttaaggtggtgggtgggact
2851 to 2925
```

FIG. 12-20

```
     SphI                                                             AcsI
     BbuI                                                             ApoI
gcatgctggacgaatacagagtatctggtcacgactgcaagaaactgggctgctaaataaatgtgagc gaattca
base pairs
cgtacgacctgcttatgtctcatagaccagtgctgacgttctttgacccgacgatttatttacactcg cttaagt
2926 to 3000
     PaeI                                                             EcoRI
     NspI

                                                                  AccB1I
                      BpmI                                         BshNI
aggtcgaaaagccagcctggaggaaatacagcttgttcattctgaacatcactcactgttgtatggcaccaaccc
base pairs
tccagcttttcggtcggacctcctttatgtcgaacaagtaagacttgtagtgagtgacaacataccgtggttggg
3001 to 3075
                      GsuI                                         BanI
                                                                  Eco64I
```

FIG. 12-21

```
                                        ErhI
                                        StyI Eco130I
 BstXI              AlwNI               EcoT14I
cctggacggacagaagctggaccccaggatactcctaggtgatgactctcaaaagtttttttcctcattaccttg
base pairs
ggacctgcctgtcttcgacctggggtcctatgaggatccactactgagagttttcaaaaaaaggagtaatggaac
3076 to 3150
                                        BssT1I
                                        AvrII
                                        BlnI

                                                        BsaWI          BsgI
tggtggacttggggtggacagtgacaccatttggaatgagctacactcgtccggtgctgcacgcatggctgttgg
base pairs
accacctgaaccccacctgtcactgtggtaaaccttactcgatgtgagcaggccacgacgtgcgtaccgacaacc
3151 to 3225
```

FIG. 12-22

```
                            CvnI
                            AocI                                        CfrI
                            Bsu36I         Eco57I             DraII    EaeI
ctgtgtcatcgagctggcttccaaagtggcctcaggagagctgaagaatgggtttgctgttgtgaggccccctgg
base pairs
gacacagtagctcgaccgaaggtttcaccggagtcctctcgacttcttacccaaacgacaacactccgggggacc
3226 to 3300
                            Eco81I                            EcoO109I
                            Bse21I

MscI                    ErhI Eco130I
                        BssT1I BstXI
             Eco57I   MslI DsaI
ccatcacgctgaagaatccacagccatggggttctgctttttaattcagttgcaattaccgccaaatacttgag
base pairs
ggtagtgcgacttcttaggtgtcggtaccccaagacgaaaaattaagtcaacgttaatggcggtttatgaactc
3301 to 3375
MluNI                   EcoT14I
BalI                    StyI BstDSI
                        NcoI Bsp19I
```

FIG. 12-23

```
                                    BstX2I          NcoI Bsp19I Asp718I   SseBI
                                    BstYI           StyI BstDSI AccB1I
                                                                       Eco147I
     BsaI                           XhoII           EcoT14I  BshNI        StuI
agaccaactaaatataagcaagatattgattgtagatctggatgttcaccatggaaacggtacccagcaggcctt
base pairs
tctggttgatttatattcgttctataactaacatctagacctacaagtggtacctttgccatgggtcgtccggaa
3376 to 3450
     Eco31I                         BglII           BssT1I   BanI KpnI    AatI
                                    MflI            ErhI Eco130I Eco64I   Pme55I
                                                    DsaI     Acc65I
```

```
                  SspBI
                  Bsp1407I               MslI               Asp700I
ttatgctgaccccagcatcctgtacatttcactccatcgctatgatgaagggaactttttccctggcagtggagc
base pairs
aatacgactggggtcgtaggacatgtaaagtgaggtagcgatactacttcccttgaaaaagggaccgtcacctcg
3451 to 3525
                  BsrGI                                     XmnI
```

FIG. 12-24

```
                    SseBI ErhI
FriOI               Eco147I
Eco24I              StuI BssT1I            SspI
cccaaatgaggttggaacaggccttggagaagggtacaatataaatattgcctggacaggtggccttgatcctcc
base pairs
gggtttactccaaccttgtccggaacctcttcccatgttatatttataacggacctgtccaccggaactaggagg
3526 to 3600
BanII               AatI StyI
                    Pme55I Eco130I
                     EcoT14I

NcoI Bsp19I                                     MscI
StyI BstDSI                 BsaMI               MluNI
                                                                  AspI
EcoT14I                     Mva1269I           EaeI
                                                                  AtsI
catgggagatgttgagtaccttgaagcattcaggaccatcgtgaagcctgtggccaaagagtttgatccagacat
base pairs
gtaccctctacaactcatggaacttcgtaagtcctggtagcacttcggacaccggtttctcaaactaggtctgta
3601 to 3675
BssT1I                      BsmI               CfrI
DsaI                                                           Tth111I
ErhI Eco130I                                      BalI
```

FIG. 12-25

```
            Mph1103I
            EcoT22I
         Ppu10I                    EcoNI
ggtcttagtatctgctggatttgatgcattggaaggccacacccctcctctaggagggtacaaagtgacggcaaa
base pairs
ccagaatcatagacgacctaaactacgtaaccttccggtgtggggaggagatcctcccatgtttcactgccgttt
3676 to 3750
            NsiI                     BseRI
            Zsp2I

          MfeI                    AflIII         XbaI
atgttttggtcatttgacgaagcaattgatgacattggctgatggacgtgtggtgttggctctagaaggaggaca
base pairs
tacaaaaccagtaaactgcttcgttaactactgtaaccgactacctgcacaccacaaccgagatcttcctcctgt
3751 to 3825
          MunI
```

FIG. 12-26

```
                    Mph1103I
                    EcoT22I
                Ppu10I                                         BpmI
tgatctcacagccatctgtgatgcatcagaagcctgtgtaaatgcccttctaggaaatgagctggagccacttgc
base pairs
actagagtgtcggtagacactacgtagtcttcggacacatttacgggaagatcctttactcgacctcggtgaacg
3826 to 3900
                    NsiI                                       GsuI
                    Zsp2I

                                BsaMI
     Asp700I                    Mva1269I                    ApoI
agaagatattctccaccaaagcccgaatatgaatgctgttatttctttacagaagatcattgaaattcaaagtat
base pairs
tcttctataagaggtggtttcgggcttatacttacgacaataaagaaatgtcttctagtaactttaagtttcata
3901 to 3975
     XmnI                       BsmI                        AcsI
```

FIG. 12-27

```
                  MflI  AccB1I                                      AvaI BcoI
                  BstI BsaWI KpnI                               MflI Eco88I PspALI
      DraI        BamHI BshNI                                   XhoII Cfr9I SmaI MslI
gtctttaaagttctctggatccggtaccagattacaaggacgacgatgacaagtagat cccgggtggcatccctg
base pairs
cagaaatttcaagagacctaggccatggtctaatgttcctgctgctactgttcatcta gggcccaccgtagggac
3976 to 4050
                  XhoII BanI Eco64I                             BstYI Ama87I
                  BstYI Acc65I                                  BstX2I  BsoBI
                  BstX2I Asp718I                                    XmaI PspAI

                           Eco130I
                           StyI                 GsuI
                           EcoT14I            MslI
tgacccctccccagtgcctctcctggccttggaagttgccactccagtgcccaccagccttgtcctaataaaatt
base pairs
actggggaggggtcacggagaggaccggaaccttcaacggtgaggtcacgggtggtcggaacaggattattttaa
4051 to 4125
                           BssT1I               BpmI
                           ErhI
```

FIG. 12-28

```
                 AspEI                                      DraII
                Eam1105I                   SspI            PspOMI
aagttgcatcattttgtctgactaggtgtcctctataatattatggggtggagggggtggtatggagcaagggg
base pairs
ttcaacgtagtaaaacagactgatccacaggagatattataataccccacctcccccaccatacctcgttcccc
4126 to 4200
                 EclHKI
                                                                  Bsp120I
                 AhdI
                                                                    EcoO1

  Eco24I          SfcI
    BanII     Bbv16II
     FriOI    BbsI     DraII                           BpmI BsgI
cccaagttgggaagacaacctgtagggcctgcggggtctattcgggaaccaagctggagtgcagtggcacaatct
base pairs
gggttcaacccttctgttggacatcccggacgccccagataagcccttggttcgacctcacgtcaccgtgttaga
4201 to 4275
              BpiI     EcoO109I                        GsuI
   09I        BpuAI
  ApaI            BstSFI
```

FIG. 12-29

```
                                                      BcoI
                                                     Ama87I
                                              BcgI    AvaI
tggctcactgcaatctccgcctcctgggttcaagcgattctcctgcctcagcctcccgagttgttgggattccag
base pairs
accgagtgacgttagaggcggaggacccaagttcgctaagaggacggagtcggagggctcaacaaccctaaggtc
4276 to 4350
                                                      Eco88I
                                                      BsoBI

     NspI       BlpI                                            MscI
    PaeI Mph1103I                                              MluNI
  Ppu10I EcoT22I                                 Esp3I        EaeI
gcatgcatgaccaggctcagctaatttttgtttttttggtagagacggggtttcaccatattggccaggctggtc
base pairs
cgtacgtactggtccgagtcgattaaaaacaaaaaaaccatctctgccccaaagtggtataaccggtccgaccag
4351 to 4425
     BbuI Zsp2I CelII                            BsmBI          CfrI
     SphI       Bsp1720I                                          BalI
       NsiI     Bpu1102I
```

FIG. 12-30

```
                                 Eco130I
                                 StyI
  BsaI                           EcoT14I             BstXI
tccaactcctaatctcaggtgatctacccaccttggcctcccaaattgctgggattacaggcgtgaaccactgct
base pairs
aggttgaggattagagtccactagatgggtggaaccggagggtttaacgaccctaatgtccgcacttggtgacga
4426 to 4500
  Eco31I                         BssT1I
                                 ErhI
```

FIG. 12-31

```
                                         BbiII
                                                         NcoI
                                         Hin1I           StyI
                 DraI                    AcyI  AatII   EcoT14I
ccttccctgtccttctgattttaaaataactataccagcaggaggacgtccagacacagcataggctacctgcc
base pairs
gggaagggacaggaagactaaaattttattgatatggtcgtcctcctgcaggtctgtgtcgtatccgatggacgg
4501 to 4575
                                         Msp17I                 BssT1I

                                                                 ErhI
                                         BsaHI
                                                                BspMI

                                         Hsp92I


   Eco130I BsrFI PflMI
   DsaI AgeI Bse118I
        BsaWI AccB7I
atggcccaaccggtgggacatttgagttgcttgcttggcactgtcctctcatgcgttgggtccactcagtagatg
base pairs
taccgggttggccaccctgtaaactcaacgaacgaaccgtgacaggagagtacgcaacccaggtgagtcatctac
4576 to 4650
        BssAI Esp1396I
   BstDSI PinAI Van91I
    Bsp19I Cfr10I
```

FIG. 12-32

```
                   EaeI     AlwNI
cctgttgaattgggtacgcggccagcttctgtggaatgtgtgtcagttagggtgtggaaagtccccaggctcccc
base pairs
ggacaacttaacccatgcgccggtcgaagacaccttacacacagtcaatcccacacctttcaggggtccgagggg
4651 to 4725
                   CfrI


                         NspI
                         PaeI Mph1103I
                       Ppu10I EcoT22I          SexAI
agcaggcagaagtatgcaaagcatgcatctcaattagtcagcaaccaggtgtggaaaagtccccaggctccccag
base pairs
tcgtccgtcttcatacgtttcgtacgtagagttaatcagtcgttggtccacaccttttcaggggtccgaggggtc
4726 to 4800
                         BbuI Zsp2I
                         SphI
                           NsiI
```

FIG. 12-33

```
                NspI
                PaeI Mph1103I
               Ppu10I EcoT22I
caggcagaagtatgcaaagcatgcatctcaattagtcagcaaccatagtcccgcccctaactccgcccatcccgc
base pairs
gtccgtcttcatacgtttcgtacgtagagttaatcagtcgttggtatcagggcggggattgaggcgggtagggcg
4801 to 4875
                BbuI Zsp2I
                SphI
                  NsiI

                            NcoI Bsp19I
                            StyI  BstDSI
                            EcoT14I
ccctaactccgcccagttccgcccattctccgccccatggctgactaattttttttatttatgcagaggccgagg
base pairs
gggattgaggcgggtcaaggcgggtaagaggcggggtaccgactgattaaaaaaaataaatacgtctccggctcc
4876 to 4950
                            BssT1I
                            ErhI Eco130I
                            DsaI
```

FIG. 12-34

```
                                                           SseBI AvrII
                                                          Eco147I  BlnI
      BglI                                BseRI            StuI BssT1I
ccgcctcggcctctgagctattccagaagtagtgaggaggcttttttggaggcctaggcttttgcaaaaagctc c
base pairs
ggcggagccggagactcgataaggtcttcatcactcctccgaaaaacctccggatccgaaaacgtttttcgagg
4951 to 5025
      SfiI                                                 AatI StyI
                                                          Pme55I  ErhI
                                                           EcoT14I Eco130I

Ama87I
Eco88I BseRI
AvaI BsoBI                               SfcI             ApoI
tcgaggaactgaaaaaccagaaagttaattccctatagtgagtcgtattaaattcgtaatcatggtcatagctgt
base pairs
agctccttgactttttggtctttcaattaagggatatcactcagcataatttaagcattagtaccagtatcgaca
5026 to 5100
XhoI BcoI                                BstSFI           AcsI
Sfr274I
PaeR7I
```

FIG. 12-35

```
                 AccBSI
                 BsrBI
ttcctgtgtgaaattgttatccgctcacaattccacacaacatacgagccggaagcataaagtgtaaagcctggg
base pairs
aaggacacactttaacaataggcgagtgttaaggtgtgttgtatgctcggccttcgtatttcacatttcggaccc
5101 to 5175
                 BstD102I


AccB1I                VspI
BshNI                 PshBI
gtgcctaatgagtgagctaactcacattaattgcgttgcgctcactgcccgctttccagtcgggaaacctgtcgt
base pairs
cacggattactcactcgattgagtgtaattaacgcaacgcgagtgacgggcgaaaggtcagccctttggacagca
5176 to 5250
BanI                  AsnI
Eco64I                AseI
```

FIG. 12-36

```
          VspI                                                          Eam1104I
     MspA1I                                                        BstH2I
     PvuII PshBI     EaeI                                          Bsp143II
gccagctgcattaatgaatcggccaacgcgcggggagaggcggtttgcgtattgggcgctcttccgcttcctcgc
base pairs
cggtcgacgtaattacttagccggttgcgcgcccctctccgccaaacgcataacccgcgagaaggcgaaggagcg
5251 to 5325
     NspBII          CfrI                                          HaeII EarI
          AsnI                                                          SapI
          AseI                                                          Ksp632I

                           BstMCI                    AccBSI
                           BsaOI                     BsrBI
tcactgactcgctgcgctcggtcgttcggctgcggcgagcggtatcagctcactcaaaggcggtaatacggttat
base pairs
agtgactgagcgacgcgagccagcaagccgacgccgctcgccatagtcgagtgagtttccgccattatgccaata
5326 to 5400
                           Bsh1285I                  BstD102I
                           BsiEI
```

FIG. 12-37

```
                                       NspI
                                  BspLU11I
ccacagaatcaggggataacgcaggaaagaacatgtgagcaaaaggccagcaaaaggccaggaaccgtaaaaagg
base pairs
ggtgtcttagtcccctattgcgtcctttcttgtacactcgttttccggtcgttttccggtccttggcatttttcc
5401 to 5475
                                  AflIII


                                                                      DrdI
ccgcgttgctggcgtttttccataggctccgcccccctgacgagcatcacaaaaatcgacgctcaagtcagaggt
base pairs
ggcgcaacgaccgcaaaaaggtatccgaggcggggggactgctcgtagtgtttttagctgcgagttcagtctcca
5476 to 5550
```

FIG. 12-38

BsiI

ggcgaaacccgacaggactataaagataccaggcgtttccccctggaagctccctcgtgcgctctcctgttccga
base pairs
ccgctttgggctgtcctgatatttctatggtccgcaaaggggaccttcgagggagcacgcgagaggacaaggct
5551 to 5625

BssSI

BstH2I
BsaWI Bsp143II SfcI
ccctgccgcttaccggatacctgtccgcctttctcccttcgggaagcgtggcgctttctcaatgctcacgctgta
base pairs
gggacggcgaatggcctatggacaggcggaaagagggaagcccttcgcaccgcgaaagagttacgagtgcgacat
5626 to 5700

HaeII BstSFI

FIG. 12-39

```
                                                         BsiHKAI
                                                                            NspBII
                                                     Alw44I                 BstMCI
                                                     VneI Bbv12I             BsaOI
ggtatctcagttcggtgtaggtcgttcgctccaagctgggctgtgtgcacgaaccccccgttcagcccgaccgct
base pairs
ccatagagtcaagccacatccagcaagcgaggttcgacccgacacacgtgcttgggggcaagtcgggctggcga
5701 to 5775
                                                     ApaLI
                                                                          Bsh1285I
                                                         AspHI               BsiEI
                                                         Alw21I
                                                                            MspA1I

         BsaWI                                                                 AlwNI
gcgccttatccggtaactatcgtcttgagtccaacccggtaagacacgacttatcgccactggcagcagccactg
base pairs
cgcggaataggccattgatagcagaactcaggttgggccattctgtgctgaatagcggtgaccgtcgtcggtgac
5776 to 5850
```

FIG. 12-40

SfcI

gtaacaggattagcagagcgaggtatgtaggcggtgctacagagttcttgaagtggtggcctaactacggctaca
base pairs
cattgtcctaatcgtctcgctccatacatccgccacgatgtctcaagaacttcaccaccggattgatgccgatgt
5851 to 5925

BstSFI

Eco57I

ctagaagaacagtatttggtatctgcgctctgctgaagccagttaccttcggaaaaagagttggtagctcttgat
base pairs
gatcttcttgtcataaaccatagacgcgagacgacttcggtcaatggaagcctttttctcaaccatcgagaacta
5926 to 6000

FIG. 12-41

```
                 NspBII                                            MflI
                                                                   XhoII
ccggcaaacaaaccaccgctggtagcggtggtttttttgtttgcaagcagcagattacgcgcagaaaaaaaggat
base pairs
ggccgtttgtttggtggcgaccatcgccaccaaaaaaacaaacgttcgtcgtctaatgcgcgtctttttttccta
6001 to 6075
                 MspA1I                                            BstYI
                                                                  BstX2I
```

```
      MflI
      XhoII
ctcaagaagatcctttgatcttttctacggggtctgacgctcagtggaacgaaaactcacgttaagggattttgg
base pairs
gagttcttctaggaaactagaaaagatgccccagactgcgagtcaccttgcttttgagtgcaattccctaaaacc
6076 to 6150
      BstYI
      BstX2I
```

FIG. 12-42

```
                      MflI        MflI
 RcaI                 XhoII       XhoII    DraI               DraI
tcatgagattatcaaaaaggatcttcacctagatccttttaaattaaaaatgaagttttaaatcaatctaaagta
base pairs
agtactctaatagtttttcctagaagtggatctaggaaaatttaatttttacttcaaaatttagttagatttcat
6151 to 6225
 BspHI                BstYI       BstYI
                      BstX2I      BstX2I
```

```
                                               AccB1I
                                               BshNI
tatatgagtaaacttggtctgacagttaccaatgcttaatcagtgaggcacctatctcagcgatctgtctatttc
base pairs
atatactcatttgaaccagactgtcaatggttacgaattagtcactccgtggatagagtcgctagacagataaag
6226 to 6300
                                               BanI
                                               Eco64I
```

FIG. 12-43

```
                           Eam1105I
                           AspEI
gttcatccatagttgcctgactccccgtcgtgtagataactacgatacgggagggcttaccatctggccccagtg
base pairs
caagtaggtatcaacggactgaggggcagcacatctattgatgctatgccctcccgaatggtagaccggggtcac
6301 to 6375
                        EclHKI
                        AhdI
```

```
                                     Cfr10I
        BsrDI         BsaI        BssAI      BpmI                           BglI
ctgcaatgataccgcgagacccacgctcaccggctccagatttatcagcaataaaccagccagccggaagggccg
base pairs
gacgttactatggcgctctgggtgcgagtggccgaggtctaaatagtcgttatttggtcggtcggccttcccggc
6376 to 6450
                     Eco31I      BsrFI     GsuI
                                 Bse118I
```

FIG. 12-44

```
                                        VspI
                                        PshBI
agcgcagaagtggtcctgcaactttatccgcctccatccagtctattaattgttgccgggaagctagagtaagta
base pairs
tcgcgtcttcaccaggacgttgaaataggcggaggtaggtcagataattaacaacggcccttcgatctcattcat
6451 to 6525
                                        AsnI
                                        AseI

                    AviII               BstSFI
                    FspI                SfcI       MslI
gttcgccagttaatagtttgcgcaacgttgttgccattgctacaggcatcgtggtgtcacgctcgtcgtttggta
base pairs
caagcggtcaattatcaaacgcgttgcaacaacggtaacgatgtccgtagcaccacagtgcgagcagcaaaccat
6526 to 6600
                    Acc16I              BsrDI
                        Psp1406I
```

FIG. 12-45

```
                BsaWI
tggcttcattcagctccggttcccaacgatcaaggcgagttacatgatcccccatgttgtgcaaaaaagcggtta
base pairs
accgaagtaagtcgaggccaagggttgctagttccgctcaatgtactagggggtacaacacgttttttcgccaat
6601 to 6675
```

```
                   BstMCI
                   PvuI BsiEI
                   BsaOI                EaeI                   MslI
gctccttcggtcctccgatcgttgtcagaagtaagttggccgcagtgttatcactcatggttatggcagcactgc
base pairs
cgaggaagccaggaggctagcaacagtcttcattcaaccggcgtcacaatagtgagtaccaataccgtcgtgacg
6676 to 6750
                   BspCI                CfrI
                   Bsh1285I
                   Ple19I
```

FIG. 12-46

```
                                                            Acc113I
                                                            Eco255I
ataattctcttactgtcatgccatccgtaagatgcttttctgtgactggtgagtactcaaccaagtcattctgag
base pairs
tattaagagaatgacagtacggtaggcattctacgaaaagacactgaccactcatgagttggttcagtaagactc
6751 to 6825
                                                            ScaI


                                          BbiII
                  BstMCI                  Hin1I
                  BsaOI    BcgI           AcyI
aatagtgtatgcggcgaccgagttgctcttgcccggcgtcaatacgggataataccgcgccacatagcagaactt
base pairs
ttatcacatacgccgctggctcaacgagaacgggccgcagttatgccctattatggcgcggtgtatcgtcttgaa
6826 to 6900
                  Bsh1285I                Msp17I
                  BsiEI                   BsaHI
                                          Hsp92I
```

FIG. 12-47

```
         Alw21I       XmnI                        MflI                MflI
 DraI    AspHI        Psp1406I                    XhoII     NspBII    XhoII
taaaagtgctcatcattggaaaacgttcttcggggcgaaaactctcaaggatcttaccgctgttgagatccagtt
base pairs
attttcacgagtagtaacctttgcaagaagccccgcttttgagagttcctagaatggcgacaactctaggtcaa
6901 to 6975
         BsiHKAI      Asp700I                     BstYI     MspA1I    BstYI
         Bbv12I                                   BstX2I              BstX2I
```

```
             BssSI
            Alw44I Bbv12I
             VneI BsiHKAI        Eco57I
cgatgtaacccactcgtgcacccaactgatcttcagcatcttttactttcaccagcgtttctgggtgagcaaaaa
base pairs
gctacattgggtgagcacgtgggttgactagaagtcgtagaaaatgaaagtggtcgcaaagacccactcgttttt
6976 to 7050
             ApaLI Alw21I
              BsiI
                AspHI
```

FIG. 12-48

```
                                                MslI                 EarI
                                                                     Eam1104I
caggaaggcaaaatgccgcaaaaaagggaataagggcgacacggaaatgttgaatactcatactcttcctttttc
base pairs
gtccttccgttttacggcgtttttcccttattcccgctgtgcctttacaacttatgagtatgagaaggaaaaag
7051 to 7125

                                                                     Ksp632I

  SspI                                           AccBSI
                                     RcaI        BsrBI
aatattattgaagcatttatcagggttattgtctcatgagcggatacatatttgaatgtatttagaaaaataaac
base pairs
ttataataacttcgtaaatagtcccaataacagagtactcgcctatgtataaacttacataaatctttttatttg
7126 to 7200

                                     BspHI       BstD102I
```

FIG. 12-49

```
                                                  SfcI
aaataggggttccgcgcacatttccccgaaaagtgccacctgacgcgccctgtagcggcgcattaagcgcggcgg
base pairs
tttatccccaaggcgcgtgtaaaggggcttttcacggtggactgcgcgggacatcgccgcgtaattcgcgccgcc
7201 to 7275
                                                  BstSFI

                                                                AccBSI
                                          BstH2I   HaeII BstD102I
                                          Bsp143II       BsrBI
gtgtggtggttacgcgcagcgtgaccgctacacttgccagcgccctagcgcccgctcctttcgctttcttccctt
base pairs
cacaccaccaatgcgcgtcgcactggcgatgtgaacggtcgcgggatcgcgggcgaggaaagcgaaagaagggaa
7276 to 7350
                                          HaeII    Bsp143II
                                                  BstH2I
```

FIG. 12-50

```
                 BsrFI
                 BssAI NaeI
                 MroNI Bse118I
cctttctcgccacgttcgccggctttccccgtcaagctctaaatcggggcatccctttagggttccgatttagtg
base pairs
ggaaagagcggtgcaagcggccgaaaggggcagttcgagatttagccccgtagggaaatcccaaggctaaatcac
7351 to 7425
                 NgoAIV
                 NgoMI
                 Cfr10I

      AccB1I
      BshNI
                                                BsaAI
ctttacggcacctcgaccccaaaaaacttgattagggtgatggttcacgtagtgggccatcgccctgatagacgg
base pairs
gaaatgccgtggagctggggttttttgaactaatcccactaccaagtgcatcacccggtagcgggactatctgcc
7426 to 7500
      BanI
      Eco64I                                       DraIII
```

FIG. 12-51

```
                    DrdI
tttttcgccctttgacgttggagtccacgttctttaatagtggactcttgttccaaactggaacaacactcaacc
base pairs
aaaaagcgggaaactgcaacctcaggtgcaagaaattatcacctgagaacaaggtttgaccttgttgtgagttgg
7501 to 7575
```

```
ctatctcggtctattcttttgatttataagggattttgccgatttcggcctattggttaaaaaatgagctgattt
base pairs
gatagagccagataagaaaactaaatattccctaaaacggctaaagccggataaccaattttttactcgactaaa
7576 to 7650
```

FIG. 12-52

```
      ApoI          ApoI              SspI  Psp1406I
aacaaaaatttaacgcgaattttaacaaaatattaaacgtttacaattt  base pairs
ttgtttttaaattgcgcttaaaattgttttataatttgcaaatgttaaa  7651 to 7699
      AcsI          AcsI
```

Table by Enzyme Name

Enzyme name	No. cuts	Positions of sites	Recognition sequence	
AatI	3	3446 3546 5002	agg/cct	More info
AatII	5	451 504 587 773 4550	gacgt/c	More info
Acc113I	1	6804	agt/act	More info
Acc16I	2	21 6546	tgc/gca	More info
Acc65I	3	2264 3434 3998	g/ gtacc	More info
AccB1I	8	791 2264 3065 3434 3998 5175 6272 7432	g/ gyrcc	More info
AccB7I	6	1445 1482 1775 1796 2644 4587	ccannnn/ntgg	More info
AccBSI	4	5126 5367 7168 7332	gagcgg	More info
AclNI	1	326	a/ ctagt	More info
AcsI	8	912 1990 2244 2994 3963 5075 7656 7667	r/ aatty	More info
AcyI	6	448 501 584 770 4547 6861	gr/cgyc	More info

FIG. 12-53

AflIII	3	2702 3796 5431	a/ crygt	More info
AgeI	1	4584	a/ ccggt	More info
AhdI	2	4150 6324	gacnnn/nngtc	More info
Alw21I	6	894 1576 2330 5749 6910 6995	gwgcw/c	More info
Alw44I	2	5745 6991	g/ tgcac	More info
AlwNI	6	1147 1273 1775 3091 4678 5847	cagnnn/ctg	More info
Ama87I	3	4034 4330 5025	c/ ycgrg	More info
AocI	3	1034 1046 3256	cc/ tnagg	More info
ApaI	1	4202	gggcc/c	More info
ApaLI	2	5745 6991	g/ tgcac	More info
ApoI	8	912 1990 2244 2994 3963 5075 7656 7667	r/ aatty	More info
AseI	4	334 5202 5261 6496	at/ taat	More info
AsnI	4	334 5202 5261 6496	at/ taat	More info
Asp700I	5	1107 2481 3506 3906 6923	gaann/nnttc	More info
Asp718I	3	2264 3434 3998	g/ gtacc	More info

FIG. 12-54

AspEI	2	4150 6324	gacnnn/nngtc	More info
AspHI	6	894 1576 2330 5749 6910 6995	gwgcw/c	More info
AspI	1	3674	gacn/nngtc	More info
AtsI	1	3674	gacn/nngtc	More info
AvaI	3	4034 4330 5025	c/ ycgrg	More info
AviII	2	21 6546	tgc/gca	More info
AvrII	2	3109 5003	c/ ctagg	More info
BalI	5	184 238 3300 3653 4414	tgg/cca	More info
BamHI	1	3992	g/ gatcc	More info
BanI	8	791 2264 3065 3434 3998 5175 6272 7432	g/ gyrcc	More info
BanII	5	894 1017 1623 3526 4202	grgcy/c	More info
BanIII	1	939	at/ cgat	More info
BbiII	6	448 501 584 770 4547 6861	gr/cgyc	More info
BbrPI	1	2705	cac/gtg	More info
BbsI	2	2512 4216	gaagac	More info
BbuI	4	2930 4355 4750 4823	gcatg/c	More info
Bbv12I	6	894 1576 2330 5749 6910 6995	gwgcw/c	More info
Bbv16II	2	2512 4216	gaagac	More info
BcgI	4	941 2556 4321 6851	cgannnnnntgc	More info

FIG. 12-55

BclI	1	969	t/ gatca	More info
BcoI	3	4034 4330 5025	c/ ycgrg	More info
BglI	5	14 417 538 4956 6444	gccnnnn/nggc	More info
BglII	2	932 3409	a/ gatct	More info
BlnI	2	3109 5003	c/ ctagg	More info
BlpI	3	1200 2337 4366	gc/tnagc	More info
BpiI	2	2512 4216	gaagac	More info
BpmI	10	1015 1279 1772 2781 2842 3022 3892 4097 4259 6414	ctggag	More info
Bpu1102I	3	1200 2337 4366	gc/tnagc	More info
Bpu14I	3	1603 1988 2423	tt/cgaa	More info
BpuAI	2	2512 4216	gaagac	More info
Bsa29I	1	939	at/ cgat	More info
BsaAI	3	666 2705 7473	yac/gtr	More info
BsaHI	6	448 501 584 770 4547 6861	gr/cgyc	More info
BsaI	3	3380 4427 6396	ggtctc	More info
BsaMI	3	1886 3631 3936	gaatgc	More info
BsaOI	7	42 424 928 5347 5771 6694 6843	cgry/cg	More info
BsaWI	6	3200 3995 4584 5637 5784 6615	w/ ccggw	More info
BscI	1	939	at/ cgat	More info

FIG. 12-56

Bse118I	3	4584 6404 7368	r/ ccggy	More info
Bse21I	3	1034 1046 3256	cc/ tnagg	More info
BseCI	1	939	at/ cgat	More info
BseRI	5	1337 1671 3725 4989 5027	gaggag	More info
BsgI	3	2315 3212 4264	gtgcag	More info
Bsh1285I	7	42 424 928 5347 5771 6694 6843	cgry/cg	More info
BshNI	8	791 2264 3065 3434 3998 5175 6272 7432	g/ gyrcc	More info
BsiEI	7	42 424 928 5347 5771 6694 6843	cgry/cg	More info
BsiHKAI	6	894 1576 2330 5749 6910 6995	gwgcw/c	More info
BsiI	2	5609 6993	ctcgtg	More info
BsmBI	3	2023 2773 4397	cgtctc	More info
BsmI	3	1886 3631 3936	gaatgc	More info
BsoBI	3	4034 4330 5025	c/ ycgrg	More info
Bsp106I	1	939	at/ cgat	More info
Bsp119I	3	1603 1988 2423	tt/cgaa	More info
Bsp120I	1	4198	g/ ggccc	More info
Bsp1407I	2	270 3471	t/ gtaca	More info
Bsp143II	5	2519 5309 5679 7318 7326	rgcgc/y	More info
Bsp1720I	3	1200 2337 4366	gc/tnagc	More info
Bsp19I	6	686 3324 3424 3600 4574 4910	c/ catgg	More info

FIG. 12-57

BspCI	2	42 6694	cgat/cg	More info
BspDI	1	939	at/ cgat	More info
BspHI	3	1891 6151 7159	t/ catga	More info
BspLU11I	1	5431	a/ catgt	More info
BspMI	2	1913 4574	acctgc	More info
BspXI	1	939	at/ cgat	More info
BsrBI	4	5126 5367 7168 7332	gagcgg	More info
BsrDI	4	245 2827 6383 6565	gcaatg	More info
BsrFI	3	4584 6404 7368	r/ ccggy	More info
BsrGI	2	270 3471	t/ gtaca	More info
BssAI	3	4584 6404 7368	r/ ccggy	More info
BssSI	2	5609 6993	ctcgtg	More info
BssT1I	13	686 1950 2226 3109 3324 3424 3547 3600 4077 4456 4574 4910 5003	c/ cwwgg	More info
BstBI	3	1603 1988 2423	tt/cgaa	More info
BstD102I	4	5126 5367 7168 7332	gagcgg	More info
BstDSI	7	686 1062 3324 3424 3600 4574 4910	c/ crygg	More info
BstH2I	5	2519 5309 5679 7318 7326	rgcgc/y	More info

FIG. 12-58

BstI	1	3992	g/ gatcc	More info
BstMCI	7	42 424 928 5347 5771 6694 6843	cgry/cg	More info
BstSFI	8	944 2144 4220 5058 5696 5887 6565 7250	c/ tryag	More info
BstSNI	1	666	tac/gta	More info
BstX2I	12	932 2400 2634 3409 3992 4030 6072 6083 6169 6181 6949 6966	r/ gatcy	More info
BstXI	3	3076 3325 4473	ccannnnn/ntgg	More info
BstYI	12	932 2400 2634 3409 3992 4030 6072 6083 6169 6181 6949 6966	r/ gatcy	More info
BstZI	1	925	c/ ggccg	More info
Bsu15I	1	939	at/ cgat	More info
Bsu36I	3	1034 1046 3256	cc/ tnagg	More info
CciNI	1	925	gc/ggccgc	More info
CelII	3	1200 2337 4366	gc/tnagc	More info
Cfr10I	3	4584 6404 7368	r/ ccggy	More info
Cfr9I	1	4034	c/ ccggg	More info
CfrI	10	152 182 236 925 3298 3651 4412 4669 5270 6712	y/ ggccr	More info
ClaI	1	939	at/ cgat	More info
Csp45I	3	1603 1988 2423	tt/cgaa	More info
CvnI	3	1034 1046 3256	cc/ tnagg	More info

FIG. 12-59

DraI	5	3981 4523 6190 6209 6901	ttt/aaa	More info
DraII	3	3291 4198 4225	rg/gnccy	More info
DraIII	1	7476	cacnnn/gtg	More info
DrdI	3	1076 5539 7520	gacnnnn/nngtc	More info
DsaI	7	686 1062 3324 3424 3600 4574 4910	c/ crygg	More info
EaeI	10	152 182 236 925 3298 3651 4412 4669 5270 6712	y/ ggccr	More info
EagI	1	925	c/ ggccg	More info
Eam1104I	5	58 2482 2793 5314 7118	ctcttc	More info
Eam1105I	2	4150 6324	gacnnn/nngtc	More info
EarI	5	58 2482 2793 5314 7118	ctcttc	More info
Ecl136II	1	892	gag/ ctc	More info
EclHKI	2	4150 6324	gacnnn/nngtc	More info
EclXI	1	925	c/ ggccg	More info
Eco105I	1	666	tac/gta	More info
Eco130I	13	686 1950 2226 3109 3324 3424 3547 3600 4077 4456 4574 4910 5003	c/ cwwgg	More info
Eco147I	3	3446 3546 5002	agg/cct	More info

FIG. 12-60

Eco24I	5	894 1017 1623 3526 4202	grgcy/c	More info
Eco255I	1	6804	agt/act	More info
Eco31I	3	3380 4427 6396	ggtctc	More info
Eco32I	1	952	gat/ atc	More info
Eco52I	1	925	c/ ggccg	More info
Eco57I	7	1210 2446 2488 3271 3314 5963 7011	ctgaag	More info
Eco64I	8	791 2264 3065 3434 3998 5175 6272 7432	g/ gyrcc	More info
Eco72I	1	2705	cac/gtg	More info
Eco81I	3	1034 1046 3256	cc/ tnagg	More info
Eco88I	3	4034 4330 5025	c/ ycgrg	More info
EcoICRI	1	892	gag/ ctc	More info
EcoNI	4	1259 1338 1684 3723	cctnn/nnnagg	More info
EcoO109I	3	3291 4198 4225	rg/gnccy	More info
EcoRI	3	912 1990 2994	g/ aattc	More info
EcoRV	1	952	gat/ atc	More info
EcoT14I	13	686 1950 2226 3109 3324 3424 3547 3600 4077 4456 4574 4910 5003	c/ cwwgg	More info
EcoT22I	5	3703 3850 4357 4752 4825	atgca/t	More info

FIG. 12-61

ErhI	13	686 1950 2226 3109 3324 3424 3547 3600 4077 4456 4574 4910 5003	c/ cwwgg	More info
Esp1396I	6	1445 1482 1775 1796 2644 4587	ccannnn/ntgg	More info
Esp3I	3	2023 2773 4397	cgtctc	More info
FauNDI	1	560	ca/ tatg	More info
FbaI	1	969	t/ gatca	More info
FriOI	5	894 1017 1623 3526 4202	grgcy/c	More info
FspI	2	21 6546	tgc/gca	More info
GsuI	10	1015 1279 1772 2781 2842 3022 3892 4097 4259 6414	ctggag	More info
HaeII	5	2519 5309 5679 7318 7326	rgcgc/y	More info
Hin1I	6	448 501 584 770 4547 6861	gr/cgyc	More info
HincII	3	311 446 842	gty/rac	More info
HindII	3	311 446 842	gty/rac	More info
HindIII	3	918 1394 2183	a/ agctt	More info
Hsp92I	6	448 501 584 770 4547 6861	gr/cgyc	More info
KpnI	3	2268 3438 4002	ggtac/c	More info
Ksp22I	1	969	t/ gatca	More info
Ksp632I	5	58 2482 2793 5314 7118	ctcttc	More info
LspI	3	1603 1988 2423	tt/cgaa	More info
MfeI	2	1091 3773	c/ aattg	More info
MflI	12	932 2400 2634 3409 3992 4030	r/gatcy	More info

FIG. 12-62

		6072 6083 6169 6181 6949 6966		
MluNI	5	184 238 3300 3653 4414	tgg/cca	More info
Mph1103I	5	3703 3850 4357 4752 4825	atgca/t	More info
MroNI	1	7368	g/ ccggc	More info
MscI	5	184 238 3300 3653 4414	tgg/cca	More info
MslI	10	691 2094 2703 3323 3489 4047 4094 6576 6735 7094	caynn/nnrtg	More info
Msp17I	6	448 501 584 770 4547 6861	gr/cgyc	More info
MspA1I	7	71 2341 2731 5255 5773 6018 6959	cmg/ckg	More info
MunI	2	1091 3773	c/ aattg	More info
Mva1269I	3	1886 3631 3936	gaatgc	More info
NaeI	1	7370	gcc/ggc	More info
NcoI	6	686 3324 3424 3600 4574 4910	c/ catgg	More info
NdeI	1	560	ca/ tatg	More info
NgoAIV	1	7368	g/ ccggc	More info
NgoMI	1	7368	g/ ccggc	More info
NotI	1	925	gc/ggccgc	More info
NsiI	5	3703 3850 4357 4752 4825	atgca/t	More info
NspBII	7	71 2341 2731 5255 5773 6018 6959	cmg/ckg	More info
NspI	5	2930 4355 4750 4823 5435	rcatg/y	More info
NspV	3	1603 1988 2423	tt/cgaa	More info
PaeI	4	2930 4355 4750 4823	gcatg/c	More info
PaeR7I	1	5025	c/ tcgag	More info

FIG. 12-63

PflMI	6	1445 1482 1775 1796 2644 4587	ccannnn/ntgg	More info
PinAI	1	4584	a/ ccggt	More info
Ple19I	2	42 6694	cgat/cg	More info
PmaCI	1	2705	cac/gtg	More info
Pme55I	3	3446 3546 5002	agg/cct	More info
PmlI	1	2705	cac/gtg	More info
Ppu10I	5	3699 3846 4353 4748 4821	a/ tgcat	More info
PshBI	4	334 5202 5261 6496	at/ taat	More info
Psp124BI	1	894	gagct/c	More info
Psp1406I	3	6550 6923 7687	aa/cgtt	More info
PspAI	1	4034	c/ccggg	More info
PspALI	1	4036	ccc/ggg	More info
PspOMI	1	4198	g/ggccc	More info
PstI	2	948 2148	ctgca/g	More info
PvuI	2	42 6694	cgat/cg	More info
PvuII	3	71 2341 5255	cag/ctg	More info
RcaI	3	1891 6151 7159	t/ catga	More info
SacI	1	894	gagct/c	More info
SapI	2	2483 5314	gctcttc	More info
ScaI	1	6804	agt/act	More info
SexAI	1	4769	a/ ccwggt	More info
SfcI	8	944 2144 4220 5058 5696 5887	c/ tryag	More info

FIG. 12-64

		6565 7250		
SfiI	1	4956	ggccnnnn/nggcc	More info
Sfr274I	1	5025	c/ tcgag	More info
SfuI	3	1603 1988 2423	tt/cgaa	More info
SmaI	1	4036	ccc/ggg	More info
SnaBI	1	666	tac/gta	More info
SpeI	1	326	a/ ctagt	More info
SphI	4	2930 4355 4750 4823	gcatg/c	More info
SseBI	3	3446 3546 5002	agg/cct	More info
SspBI	2	270 3471	t/ gtaca	More info
SspI	6	179 226 3571 4164 7128 7681	aat/att	More info
SstI	1	894	gagct/c	More info
StuI	3	3446 3546 5002	agg/cct	More info
StyI	13	686 1950 2226 3109 3324 3424 3547 3600 4077 4456 4574 4910 5003	c/ cwwgg	More info
Tth111I	1	3674	gacn/nngtc	More info
Van91I	6	1445 1482 1775 1796 2644 4587	ccannnn/ntgg	More info
VneI	2	5745 6991	g/ tgcac	More info
VspI	4	334 5202 5261 6496	at/ taat	More info
XbaI	1	3811	t/ ctaga	More info
XcmI	2	1948 2897	ccannnnn/nnnntgg	More info

FIG. 12-65

XhoI	1	5025	c/ tcgag	More info
XhoII	12	932 2400 2634 3409 3992 4030 6072 6083 6169 6181 6949 6966	r/ gatcy	More info
XmaI	1	4034	c/ ccggg	More info
XmaIII	1	925	c/ ggccg	More info
XmnI	5	1107 2481 3506 3906 6923	gaann/nnttc	More info
Zsp2I	5	3703 3850 4357 4752 4825	atgca/t	More info

The following endonucleases were selected but don't cut this sequence:
AccI, AccIII, AfeI, AflII, Aor51HI, AscI, BbeI, BfrI, BsaBI, Bse8I, BseAI, BsePI, Bsh1365I, BsiMI, BsiWI, Bsp13I, Bsp68I, BspEI, BspTI, BsrBRI, BssHII, Bst1107I, Bst98I, BstEII, BstPI, Cfr42I, CpoI, CspI, Eco47III, Eco91I, Eco065I, EheI, FseI, HpaI, KasI, Kpn2I, KspI, MamI, MluI, MroI, MspCI, NarI, NheI, NruI, PacI, Pfl23II, PmeI, PpuMI, PshAI, Psp5II, PspEI, PspLI, PstNHI, RsrII, SacII, SalI, SbfI, Sfr303I, SgfI, SgrAI, SmiI, SplI, SrfI, Sse8387I, SstII, SunI, SwaI, Vha464I

FIG. 12-66

FIG. 13A
FIG. 13B
FIG. 13C
FIG. 13D
FIG. 13E

FIG. 13

cccattcgccattcaggctgcgcaactgttgggaagggcgatcggtgcgggcctcttcgctattacgccagctggcgaaaggg
ggatgtgctgcaaggcgattaagttgggtaacgccagggttttcccagtcacgacgttgtaaaacgacggccagtgccaagct
gatctaatcaatattggccattagccatattattcattggttatatagcataaatcaatattggctattggccattgcatacgttgtatcca
tatcataatatgtacatttatattggctcatgtccaacattaccgccatgttgacattgattattgactagttattaatagtaatcaattacg
gggtcattagttcatagcccatatatggagttccgcgttacataacttacggtaaatggcccgcctggcgaccgcccagcgaccc
ccgcccgttgacgtcaatagtgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacg
gtaaactgcccacttggcagtacatcaagtgtatcatatgccaagtccgccccctattgacgtcaatgacggtaaatggcccgcct
agcattatgcccagtacatgaccttacgggagtttcctacttggcagtacatctacgtattagtcatcgctattaccatggtgatgcg
gttttggcagtacaccaatgggcgtggatagcggtttgactcacggggatttccaagtctccaccccattgacgtcaatgggagtt
tgttttggcaccaaaatcaacgggactttccaaaatgtcgtaataaccccgccccgttgacgcaaatgggcggtaggcgtgtacg
gtgggaggtctatataagcagagctcgtttagtgaaccgtcagaattcaagcttgcggccgcagatctatcgatctgcaggatatc
(EcoRV)
acc

FIG. 13A

ATGCACAGTATGATCAGCTCAGTGGATGTGAAGTCAGAAGTTCCTGTGGGCCTGGAGCCCATCTCACCTTTA
GACCTAAGGACAGACCTCAGGATGATGATGCCCGTGGTGGACCCTGTTGTCCGTGAGAAGCAATTGCAGCAG
GAATTACTTCTTATCCAGCAGCAGCAACAAATCCAGAAGCAGCTTCTGATAGCAGAGTTTCAGAAACAGCAT
GAGAACTTGACACGGCAGCACCAGGCTCAGCTTCAGGAGCATATCAAGGAACTTCTAGCCATAAAACAGCAA
CAAGAACTCCTAGAAAAGGAGCAGAAACTGGAGCAGCAGAGGCAAGAACAGGAAGTAGAGAGGCATCGCAGA
GAACAGCAGCTTCCTCCTCTCAGAGGCAAAGATAGAGGACGAGAAAGGGCAGTGGCAAGTACAGAAGTAAAG
CAGAAGCTTCAAGAGTTCCTACTGAGTAAATCAGCAACGAAAGACACTCCAACTAATGGAAAAAATCATTCC
GTGAGCCGCCATCCCAAGCTCTGGTACACGGCTGCCCACCACACATCATTGGATCAAAGCTCTCCACCCCTT
AGTGGAACATCTCCATCCTACAAGTACACATTACCAGGAGCACAAGATGCAAAGGATGATTTCCCCCTTCGA
AAAACTGCCTCTGAGCCCAACTTGAAGGTGCGGTCCAGGTTAAAACAGAAAGTGGCAGAGAGGAGAAGCAGC
CCCTTACTCAGGCGGAAGGATGGAAATGTTGTCACTTCATTCAAGAAGCGAATGTTTGAGGTGACAGAATCC
TCAGTCAGTAGCAGTTCTCCAGGCTCTGGTCCCAGTTCACCAAACAATGGGCCAACTGGAAGTGTTACTGAA
AATGAGACTTCGGTTTTGCCCCCTACCCCTCATGCCGAGCAAATGGTTTCACAGCAACGCATTCTAATTCAT
GAAGATTCCATGAACCTGCTAAGTCTTTATACCTCTCCTTCTTTGCCCAACATTACCTTGGGGCTTCCCGCA
GTGCCATCCCAGCTCAATGCTTCGAATTCACTCAAAGAAAAGCAGAAGTGTGAGACGCAGACGCTTAGGCAA
GGTGTTCCTCTGCCTGGGCAGTATGGAGGCAGCATCCCGGCATCTTCCAGCCACCCTCATGTTACTTTAGAG
GGAAAGCCACCCAACAGCAGCCACCAGGCTCTCCTGCAGCATTTATTATTGAAAGAACAAATGCGACAGCAA
AAGCTTCTTGTAGCTGGTGGAGTTCCCTTACATCCTCAGTCTCCCTTGGCAACAAAAGAGAGAATTTCACCT
GGCATTAGAGGTACCCACAAATTGCCCCGTCACAGACCCCTGAACCGAACCCAGTCTGCACCTTTGCCTCAG
AGCACGTTGGCTCAGCTGGTCATTCAACAGCAACACCAGCAATTCTTGGAGAAGCAGAAGCAATACCAGCAG
CAGATCCACATGAACAAACTGCTTTCGAAATCTATTGAACAACTGAAGCAACCAGGCAGTCACCTTGAGGAA
GCAGAGGAAGAGCTTCAGGGGGACCAGGCGATGCAGGAAGACAGAGCGCCCTCTAGTGGCAACAGCACTAGG
AGCGACAGCAGTGCTTGTGTGGATGACACACTGGGACAAGTTGGGGCTGTGAAGGTCAAGGAGGAACCAGTG
GACAGTGATGAAGATGCTCAGATCCAGGAAATGGAATCTGGGGAGCAGGCTGCTTTTATGCAACAGCCTTTC

FIG. 13B

CTGGAACCCACGCACACACGTGCGCTCTCTGTGCGCCAAGCTCCGCTGGCTGCGGTTGGCATGGATGGATTA
GAGAAACACCGTCTCGTCTCCAGGACTCACTCTTCCCCTGCTGCCTCTGTTTTACCTCACCCAGCAATGGAC
CGCCCCCTCCAGCCTGGCTCTGCAACTGGAATTGCCTATGACCCCTTGATGCTGAAACACCAGTGCGTTTGT
GGCAATTCCACCACCCACCCTGAGCATGCTGGACGAATACAGAGTATCTGGTCACGACTGCAAGAAACTGGG
CTGCTAAATAAATGTGAGCGAATTCAAGGTCGAAAAGCCAGCCTGGAGGAAATACAGCTTGTTCATTCTGAA
CATCACTCACTGTTGTATGGCACCAACCCCCTGGACGGACAGAAGCTGGACCCCAGGATACTCCTAGGTGAT
GACTCTCAAAAGTTTTTTTCCTCATTACCTTGTGGTGGACTTGGGGTGGACAGTGACACCATTTGGAATGAG
CTACACTCGTCCGGTGCTGCACGCATGGCTGTTGGCTGTGTCATCGAGCTGGCTTCCAAAGTGGCCTCAGGA
GAGCTGAAGAATGGGTTTGCTGTTGTGAGGCCCCCTGGCCATCACGCTGAAGAATCCACAGCCATGGGGTTC
TGCTTTTTTAATTCAGTTGCAATTACCGCCAAATACTTGAGAGACCAACTAAATATAAGCAAGATATTGATT
GTAGATCTGGATGTTCACCATGGAAACGGTACCCAGCAGGCCTTTTATGCTGACCCCAGCATCCTGTACATT
TCACTCCATCGCTATGATGAAGGGAACTTTTTCCCTGGCAGTGGAGCCCCAAATGAGGTTCGGTTTATTTCT
TTAGAGCCCCACTTTTATTTGTATCTTTCAGGTAATTGCATTGCA

FIG. 13C

(BamHI)ggatccggtaccagattacaaggacgacgatgacaagtagatcccgggtggcatccctgtgacccctccccagtg
cctctcctggccttggaagttgccactccagtgcccaccagccttgtcctaataaaattaagttgcatcattttgtctgactaggtgtc
ctctataatattatggggtggaggggggtggtatggagcaaggggcccaagttgggaagacaacctgtagggcctgcggggtc
tattcgggaaccaagctggagtgcagtggcacaatcttggctcactgcaatctccgcctcctgggttcaagcgattctcctgcctc
agcctcccgagttgttgggattccaggcatgcatgaccaggctcagctaatttttgtttttttggtagagacggggtttcaccatattg
gccaggctggtctccaactcctaatctcaggtgatctacccaccttggcctcccaaattgctgggattacaggcgtgaaccactgc
tcccttccctgtccttctgattttaaaataactataccagcaggaggacgtccagacacagcataggctacctgccatggcccaac
cggtgggacatttgagttgcttgcttggcactgtcctctcatgcgttgggtccactcagtagatgcctgttgaattgggtacgcggc
cagcttctgtggaatgtgtgtcagttagggtgtggaaagtccccaggctccccagcaggcagaagtatgcaaagcatgcatctca
attagtcagcaaccaggtgtggaaagtccccaggctccccagcaggcagaagtatgcaaagcatgcatctcaattagtcagca
accatagtcccgcccctaactccgcccatcccgcccctaactccgcccagttccgcccattctccgccccatggctgactaattttt
tttatttatgcagaggccgaggccgcctcggcctctgagctattccagaagtagtgaggaggcttttttggaggcctaggcttttgc
aaaaagctcctcgaggaactgaaaaaccagaaagttaattccctatagtgagtcgtattaaattcgtaatcatggtcatagctgtttc
ctgtgtgaaattgttatccgctcacaattccacacaacatacgagccggaagcataaagtgtaaagcctggggtgcctaatgagt
gagctaactcacattaattgcgttgcgctcactgcccgctttccagtcgggaaacctgtcgtgccagctgcattaatgaatcggcc
aacgcgcggggagaggcggtttgcgtattgggcgctcttccgcttcctcgctcactgactcgctgcgctcggtcgttcggctgcg
gcgagcggtatcagctcactcaaaggcggtaatacggttatccacagaatcaggggataacgcaggaaagaacatgtgagca
aaaggccagcaaaaggccaggaaccgtaaaaaggccgcgttgctggcgtttttccataggctccgcccccctgacgagcatca
caaaaatcgacgctcaagtcagaggtggcgaaacccgacaggactataaagataccaggcgtttccccctggaagctccctcg
tgcgctctcctgttccgaccctgccgcttaccggatacctgtccgcctttctcccttcgggaagcgtggcgctttctcaatgctcac
gctgtaggtatctcagttcggtgtaggtcgttcgctccaagctgggctgtgtgcacgaaccccccgttcagcccgaccgctgcgc
cttatccggtaactatcgtcttgagtccaacccggtaagacacgacttatcgccactggcagcagccactggtaacaggattagc
agagcgaggtatgtaggcggtgctacagagttcttgaagtggtggcctaactacggctacactagaagaacagtatttggtatct
gcgctctgctgaagccagttaccttcggaaaaagagttggtagctcttgatccggcaaacaaaccaccgctggtagcggtggttt

FIG. 13D

ttttgtttgcaagcagcagattacgcgcagaaaaaaaggatctcaagaagatcctttgatcttttctacggggtctgacgctcagtg
gaacgaaaactcacgttaagggattttggtcatgagattatcaaaaaggatcttcacctagatccttttaaattaaaaatgaagtttta
aatcaatctaaagtatatatgagtaaacttggtctgacagttaccaatgcttaatcagtgaggcacctatctcagcgatctgtctatttc
gttcatccatagttgcctgactccccgtcgtgtagataactacgatacgggagggcttaccatctggccccagtgctgcaatgata
ccgcgagacccacgctcaccggctccagatttatcagcaataaaccagccagccggaagggccgagcgcagaagtggtcct
gcaactttatccgcctccatccagtctattaattgttgccgggaagctagagtaagtagttcgccagttaatagtttgcgcaacgttgt
tgccattgctacaggcatcgtggtgtcacgctcgtcgtttggtatggcttcattcagctccggttcccaacgatcaaggcgagttac
atgatcccccatgttgtgcaaaaaagcggttagctccttcggtcctccgatcgttgtcagaagtaagttggccgcagtgttatcact
catggttatggcagcactgcataattctcttactgtcatgccatccgtaagatgcttttctgtgactggtgagtactcaaccaagtcatt
ctgagaatagtgtatgcggcgaccgagttgctcttgcccggcgtcaatacgggataataccgcgccacatagcagaactttaaaa
gtgctcatcattggaaaacgttcttcggggcgaaaactctcaaggatcttaccgctgttgagatccagttcgatgtaacccactcgt
gcacccaactgatcttcagcatcttttactttcaccagcgtttctgggtgagcaaaaacaggaaggcaaaatgccgcaaaaaagg
gaataagggcgacacggaaatgttgaatactcatactcttcctttttcaatattattgaagcatttatcagggttattgtctcatgagcg
gatacatatttgaatgtatttagaaaaataaacaaataggggttccgcgcacatttccccgaaaagtgccacctgacgcgccctgt
agcggcgcattaagcgcggcgggtgtggtggttacgcgcagcgtgaccgctacacttgccagcgccctagcgcccgctccttt
cgctttcttcccttcctttctcgccacgttcgccggctttccccgtcaagctctaaatcggggcatccctttagggttccgatttagtgc
tttacggcacctcgaccccaaaaaacttgattagggtgatggttcacgtagtgggccatcgccctgatagacggtttttcgcccttt
gacgttggagtccacgttctttaatagtggactcttgttccaaactggaacaacactcaaccctatctcggtctattcttttgatttataa
gggattttgccgatttcggcctattggttaaaaaatgagctgatttaacaaaaatttaacgcgaattttaacaaaatattaaacgtttac
aattt

FIG. 13E

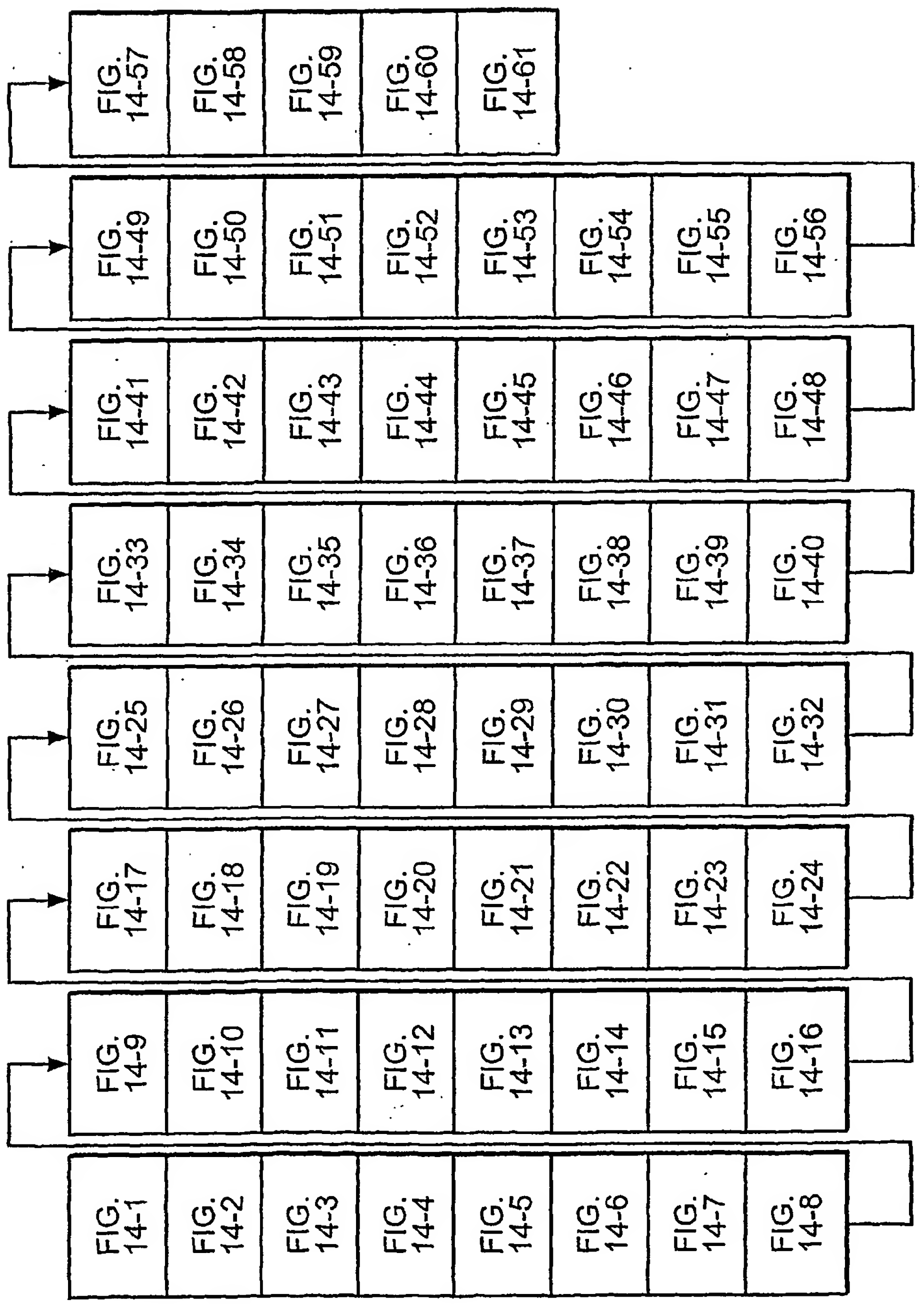
FIG. 14-1
FIG. 14-2
FIG. 14-3
FIG. 14-4
FIG. 14-5
FIG. 14-6
FIG. 14-7
FIG. 14-8
FIG. 14-9
FIG. 14-10
FIG. 14-11
FIG. 14-12
FIG. 14-13
FIG. 14-14
FIG. 14-15
FIG. 14-16
FIG. 14-17
FIG. 14-18
FIG. 14-19
FIG. 14-20
FIG. 14-21
FIG. 14-22
FIG. 14-23
FIG. 14-24
FIG. 14-25
FIG. 14-26
FIG. 14-27
FIG. 14-28
FIG. 14-29
FIG. 14-30
FIG. 14-31
FIG. 14-32
FIG. 14-33
FIG. 14-34
FIG. 14-35
FIG. 14-36
FIG. 14-37
FIG. 14-38
FIG. 14-39
FIG. 14-40
FIG. 14-41
FIG. 14-42
FIG. 14-43
FIG. 14-44
FIG. 14-45
FIG. 14-46
FIG. 14-47
FIG. 14-48
FIG. 14-49
FIG. 14-50
FIG. 14-51
FIG. 14-52
FIG. 14-53
FIG. 14-54
FIG. 14-55
FIG. 14-56
FIG. 14-57
FIG. 14-58
FIG. 14-59
FIG. 14-60
FIG. 14-61

FIG. 14

pFLAG-CMV-5b-HDAC9a

7303 base pairs

Graphic map | Table by enzyme name

```
                                      BstMCI
                AviII                    PvuI BsiEI        EarI          MspA1I
          BglI  FspI                     BsaOI             Eam1104I      PvuII
cccattcgccattcaggctgcgcaactgttgggaagggcgatcggtgcgggcctcttcgctattacgccagctgg
base pairs
gggtaagcggtaagtccgacgcgttgacaacccttcccgctagccacgcccggagaagcgataatgcggtcgacc
1 to 75
                Acc16I                   BspCI             Ksp632I       NspBII
                                         Bsh1285I
                                         Ple19I
```

FIG. 14-1

```
cgaaagggggatgtgctgcaaggcgattaagttgggtaacgcccagggttttcccagtcacgacgttgtaaaacg
base pairs
gctttcccctacacgacgttccgctaattcaacccattgcgggtcccaaaagggtcagtgctgcaacattttgc
76 to 150

                                   MscI
                                 CfrI
  EaeI                        SspI MluNI
acggccagtgccaagctgatctaatcaatattggccattagccatattattcattggttatatagcataaatcaa
base pairs
tgccggtcacggttcgactagattagttataaccggtaatcggtataataagtaaccaatatatcgtatttagtt
151 to 225
  CfrI                           EaeI
                                   BalI
```

FIG. 14-2

```
                MscI
                MluNI                                  SspBI
 SspI         EaeI      BsrDI                          Bsp1407I
tattggctattggccattgcatacgttgtatccatatcataatatgtacatttatattggctcatgtccaacatt
base pairs
ataaccgataaccggtaacgtatgcaacataggtatagtattatacatgtaaatataaccgagtacaggttgtaa
226 to 300
              CfrI                                     BsrGI
                BalI
```

```
                                       VspI
              HincII         SpeI      PshBI
accgccatgttgacattgattattgactagttattaatagtaatcaattacggggtcattagttcatagcccata
base pairs
tggcggtacaactgtaactaataactgatcaataattatcattagttaatgccccagtaatcaagtatcgggtat
301 to 375
              HindII         AclNI     AsnI
                                       AseI
```

FIG. 14-3

```
                                                            HinlI
                                        BstMCI               AcyI
                                   BglI BsaOI               HincII
tatggagttccgcgttacataacttacggtaaatggcccgcctggcgaccgcccagcgacccccgcccgttgacg
base pairs
atacctcaaggcgcaatgtattgaatgccatttaccgggcggaccgctggcgggtcgctgggggcgggcaactgc
376 to 450
                                        Bsh1285I             HindII
                                        BsiEI                Hsp92I
                                                             Msp17I

  BsaHI                                   BbiII
  AatII                                  HinlI
  BbiII                                   AcyI AatII
tcaatagtgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacgg
base pairs
agttatcactgcatacaagggtatcattgcggttatccctgaaaggtaactgcagttacccacctcataaatgcc
451 to 525
                                         Msp17I
                                          BsaHI
                                         Hsp92I
```

FIG. 14-4

```
                  BglI                            NdeI                               BbiII
                                                                                     Hin1I
                                                                                     AcyI AatII
taaactgcccacttggcagtacatcaagtgtatcatatgccaagtccgccccctattgacgtcaatgacggtaaa
base pairs
atttgacgggtgaaccgtcatgtagttcacatagtatacggttcaggcgggggataactgcagttactgccattt
526 to 600
                                                  FauNDI                             Msp17I
                                                                                     BsaHI
                                                                                     Hsp92I

                                                                                             BstSNI
                                                                                             SnaBI
tggcccgcctagcattatgcccagtacatgaccttacgggagtttcctacttggcagtacatctacgtattagtc
base pairs
accgggcggatcgtaatacgggtcatgtactggaatgccctcaaaggatgaaccgtcatgtagatgcataatcag
601 to 675
                                                                                             BsaAI
                                                                                             Eco105I
```

FIG. 14-5

```
          NcoI Bsp19I
          StyI BstDSI
          EcoT14I
atcgctattaccatggtgatgcggttttggcagtacaccaatgggcgtggatagcggtttgactcacggggattt
base pairs
tagcgataatggtaccactacgccaaaaccgtcatgtggttacccgcacctatcgccaaactgagtgcccctaaa
676 to 750
          BssT1I
          ErhI Eco130I
          DsaI MslI

                  BbiII
                  Hin1I                 AccB1I
                  AcyI AatII            BshNI
ccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatgtcgt
base pairs
ggttcagaggtggggtaactgcagttaccctcaaacaaaaccgtggttttagttgccctgaaaggttttacagca
751 to 825
                  Msp17I                BanI
                  BsaHI                 Eco64I
                  Hsp92I
```

FIG. 14-6

```
                  HincII                                                        Eco24I
                                                                               EcoICRI
aataaccccgccccgttgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagca gagctcgttta
base pairs
ttattggggcggggcaactgcgtttacccgccatccgcacatgccaccctccagatatattcgt ctcgagcaaat
826 to 900
                  HindII                                                       Ecl136II
                                                                               Bbv12I
                                                                               AspHI
                                                                               Psp124BI
SacI
FriOI
SstI
BanII
BsiHKAI                    EagI XmaIII BstYI BspDI BcgI Eco32I
            AcsI           CciNI Bsh1285I BstX2I BanIII PstI                   BclI
            ApoI  HindIII BstZI BstMCI MflI Bsa29I SfcI                        Ksp22I
gtgaaccgtcagaattcaagcttgcggccgcagatctatcgatctgcaggatatcaccatgcacagtatgatcag
base pairs
cacttggcagtcttaagttcgaacgccggcgtctagatagctagacgtcctatagtggtacgtgtcatactagtc
901 to 975
            EcoRI          EaeI Eco52I BglII BscI BspXI BstSFI                 FbaI
                           CfrI EclXI BsiEI BseCI Bsu15I EcoRV
Alw21I                     NotI BsaOI XhoII ClaI Bsp106I
```

FIG. 14-7

```
                                  FriOI            CvnI        CvnI
                                 Eco24I            AocI        AocI
                                BpmI              Bsu36I      Bsu36I
ctcagtggatgtgaagtcagaagttcctgtgggcctggagcccatctcacctttagacctaaggacagacctcag
base pairs
gagtcacctacacttcagtcttcaaggacacccggacctcgggtagagtggaaatctggattcctgtctggagtc
976 to 1050
                                GsuI              Eco81I      Eco81I
                                  BanII           Bse21I      Bse21I


            DsaI          DrdI          MfeI          Asp700I
gatgatgatgcccgtggtggaccctgttgtccgtgagaagcaattgcagcaggaattacttcttatccagcagca
base pairs
ctactactacgggcaccacctgggacaacaggcactcttcgttaacgtcgtccttaatgaagaataggtcgtcgt
1051 to 1125
            BstDSI                      MunI          XmnI
```

FIG. 14-8

```
                        AlwNI
gcaacaaatccagaagcagcttctgatagcagagtttcagaaacagcatgagaacttgacacggcagcaccaggc
base pairs
cgttgtttaggtcttcgtcgaagactatcgtctcaaagtctttgtcgtactcttgaactgtgccgtcgtggtccg
1126 to 1200
```

```
BlpI
CelII    Eco57I                                           EcoNI     AlwNI
tcagcttcaggagcatatcaaggaacttctagccataaaacagcaacaagaactcctagaaaggagcagaaact
base pairs
agtcgaagtcctcgtatagttccttgaagatcggtattttgtcgttgttcttgaggatctttcctcgtctttga
1201 to 1275
Bsp1720I
Bpu1102I
```

FIG. 14-9

```
    BpmI                                                                  BseRI
ggagcagcagaggcaagaacaggaagtagagaggcatcgcagagaacagcagcttcctcctctcagaggcaaaga
base pairs
cctcgtcgtctccgttcttgtccttcatctctccgtagcgtctcttgtcgtcgaaggaggagagtctccgtttct
1276 to 1350
    GsuI                                                                   EcoNI

                                                    HindIII
tagaggacgagaaagggcagtggcaagtacagaagtaaagcag aagcttcaagagttcctactgagtaaatcagc
base pairs
atctcctgctctttcccgtcaccgttcatgtcttcatttcgtc ttcgaagttctcaaggatgactcatttagtcg
1351 to 1425
```

FIG. 14-10

```
            Van91I                                    Van91I
            AccB7I                                    AccB7I
aacgaaagacactccaactaatggaaaaatcattccgtgagccgccatcccaagctctggtacacggctgccca
base pairs
ttgctttctgtgaggttgattaccttttttagtaaggcactcggcggtagggttcgagaccatgtgccgacgggt
1426 to 1500
            Esp1396I                                  Esp1396I
            PflMI                                     PflMI
```

```
ccacacatcattggatcaaagctctccaccccttagtggaacatctccatcctacaagtacacattaccaggagc
base pairs
ggtgtgtagtaacctagtttcgagaggtggggaatcaccttgtagaggtaggatgttcatgtgtaatggtcctcg
1501 to 1575
```

FIG. 14-11

```
 Alw21I                                  BstBI
 AspHI                                   Bpu14I                 FriOI
                                         Csp45I                 Eco24I
acaagatgcaaaggatgatttccccccttcgaaaaactgcctctgagcccaacttgaaggtgcggtccaggttaaa
base pairs
tgttctacgtttcctactaaagggggaagcttttgacggagactcgggttgaacttccacgccaggtccaattt
1576 to 1650
 BsiHKAI                                 SfuI Bsp119I           BanII
 Bbv12I                                  NspV
                                         LspI

                               BseRI          EcoNI
acagaaagtggcagagaggagaagcagccccttactcaggcggaaggatggaaatgttgtcacttcattcaagaa
base pairs
tgtctttcaccgtctctcctcttcgtcggggaatgagtccgccttcctacctttacaacagtgaagtaagttctt
1651 to 1725
```

FIG. 14-12

```
                                           Van91I
                                           AccB7I                 Van91I
                                       BpmI PflMI                  AccB7I
gcgaatgtttgaggtgacagaatcctcagtcagtagcagttctccaggctctggtcccagttcaccaaacaatgg
base pairs
cgcttacaaactccactgtcttaggagtcagtcatcgtcaagaggtccgagaccagggtcaagtggtttgttacc
1726 to 1800
                                       GsuI

                                                               Esp1396I
                                                                 PflMI
                                           AlwNI

                                          Esp1396I
```

```
gccaactggaagtgttactgaaaatgagacttcggttttgcccctacccctcatgccgagcaaatggtttcaca
base pairs
cggttgaccttcacaatgacttttactctgaagccaaaacgggggatggggagtacggctcgtttaccaaagtgt
1801 to 1875
```

FIG. 14-13

```
          BsaMI
          Mva1269I                       BspMI                             XcmI
gcaacgcattctaattcatgaagattccatgaacctgctaagtctttatacctctccttctttgcccaacattac
base pairs
cgttgcgtaagattaagtacttctaaggtacttggacgattcagaaatatggagaggaagaaacgggttgtaatg
1876 to 1950
          BsmI RcaI
               BspHI


ErhI                                  BstBI AcsI
BssT1I                                Bpu14I
                                      Csp45I
                                                                      Esp3I
cttggggcttcccgcagtgccatcccagctcaatgcttc gaattcactcaaagaaaagcagaagtgtgagacgca
base pairs
gaaccccgaagggcgtcacggtagggtcgagttacgaag cttaagtgagtttcttttcgtcttcacactctgcgt
1951 to 2025
EcoT14I                               SfuI Bsp119I
                                                                      BsmBI
StyI                                  NspV ApoI
Eco130I                               LspI EcoRI
```

FIG. 14-14

```
                                                                           MslI
gacgcttaggcaaggtgttcctctgcctgggcagtatggaggcagcatcccggcatcttccagccaccctcatgt
base pairs
ctgcgaatccgttccacaaggagacggacccgtcatacctccgtcgtagggccgtagaaggtcggtgggagtaca
2026 to 2100

                                               PstI
                                            SfcI
tactttagagggaaagccacccaacagcagccaccaggctctc ctgcagcatttattattgaaagaacaaatgcg
base pairs
atgaaatctccctttcggtgggttgtcgtcggtggtccgagag gacgtcgtaaataataactttcttgtttacgc
2101 to 2175
                                            BstSFI
```

FIG. 14-15

```
       HindIII                                          Eco130I
                                                         StyI
                                                         EcoT14I          ApoI
acagcaaaagcttcttgtagctggtggagttcccttacatcctcagtctcccttggcaacaaaagagagaatttc
base pairs
tgtcgttttcgaagaacatcgaccacctcaagggaatgtaggagtcagagggaaccgttgttttctctcttaaag
2176 to 2250
                                                         BssT1I           AcsI
                                                          ErhI

              Asp718I
              Acc65I
              BshNI                                                    BsgI
acctggcattagaggtacccacaaattgccccgtcacagacccctgaaccgaacccagtctgcacctttgcctca
base pairs
tggaccgtaatctccatgggtgtttaacggggcagtgtctggggacttggcttgggtcagacgtggaaacggagt
2251 to 2325
              BanI KpnI
              AccB1I
              Eco64I
```

FIG. 14-16

```
            Bpu1102I
     Alw21I Bsp1720I
     AspHI  CelII
gagcacgttggctcagctggtcattcaacagcaacaccagcaattcttggagaagcagaagcaataccagcagca
base pairs
ctcgtgcaaccgagtcgaccagtaagttgtcgttgtggtcgttaagaacctcttcgtcttcgttatggtcgtcgt
2326 to 2400
     BsiHKAI     PvuII
     Bbv12I BlpI MspA1I
                 NspBII


                        BstBI
MflI                    Bpu14I
XhoII                   Csp45I
                                             Eco57I
gatccacatgaacaaactgctttcgaaatctattgaacaactgaagcaaccaggcagtcaccttgaggaagcaga
base pairs
ctaggtgtacttgtttgacgaaagctttagataacttgttgacttcgttggtccgtcagtggaactccttcgtct
2401 to 2475
BstYI                   SfuI Bsp119I
BstX2I                  NspV
                        LspI
```

FIG. 14-17

```
   EarI
   Eam1104I                          Bbv16II
  Asp700I                            BbsI   Bsp143II
ggaagagcttcaggggaccaggcgatgcaggaagacagagcgccctctagtggcaacagcactaggagcgacag
base pairs
ccttctcgaagtcccctggtccgctacgtccttctgtctcgcgggagatcaccgttgtcgtgatcctcgctgtc
2476 to 2550
  XmnI   Eco57I                      BpiI   HaeII
   Ksp632I                           BpuAI  BstH2I
    SapI

  BcgI
cagtgcttgtgtggatgacacactgggacaagttggggctgtgaaggtcaaggaggaaccagtggacagtgatga
base pairs
gtcacgaacacacctactgtgtgaccctgttcaaccccgacacttccagttcctccttggtcacctgtcactact
2551 to 2625
```

FIG. 14-18

```
       MflI      Van91I
       XhoII     AccB7I
agatgctcagatccaggaaatggaatctggggagcaggctgctttatgcaacagcctttcctggaacccacgca
base pairs
tctacgagtctaggtcctttaccttagacccctcgtccgacgaaatacgttgtcggaaaggaccttgggtgcgt
2626 to 2700
       BstYI     Esp1396I
       BstX2I    PflMI


    PmaCI
    PmlI
  AflIII                       NspBII
                                                                     Esp3I
cacacgtgcgctctctgtgcgccaagctccgctggctgcggttggcatggatggattagagaaacaccgtctcgt
base pairs
gtgtgcacgcgagagacacgcggttcgaggcgaccgacgccaaccgtacctacctaatctctttgtggcagagca
2701 to 2775
   MslI Eco72I                 MspA1I
                                                                     BsmBI
    BsaAI
    BbrPI
```

FIG. 14-19

```
     BpmI          EarI
                   Eam1104I                              BsrDI          BpmI
ctccaggactcactcttcccctgctgcctctgttttacctcacccagcaatggaccgcccctccagcctggctc
base pairs
gaggtcctgagtgagaaggggacgacggagacaaaatggagtgggtcgttacctggcgggggaggtcggaccgag
2776 to 2850
     GsuI          Ksp632I                                              GsuI
```

```
                                              XcmI
tgcaactggaattgcctatgaccccttgatgctgaaacaccagtgcgtttgtggcaattccaccacccaccctga
base pairs
acgttgaccttaacggatactggggaactacgactttgtggtcacgcaaacaccgttaaggtggtgggtgggact
2851 to 2925
```

FIG. 14-20

```
    SphI                                                           AcsI
    BbuI                                                           ApoI
gcatgctggacgaatacagagtatctggtcacgactgcaagaaactgggctgctaaataaatgtgagc gaattca
base pairs
cgtacgacctgcttatgtctcatagaccagtgctgacgttctttgacccgacgatttatttacactcg cttaagt
2926 to 3000
    PaeI
    NspI                                                           EcoRI
```

```
                BpmI                                           AccB1I
                                                               BshNI
aggtcgaaaagccagcctggaggaaatacagcttgttcattctgaacatcactcactgttgtatggcaccaaccc
base pairs
tccagcttttcggtcggacctcctttatgtcgaacaagtaagacttgtagtgagtgacaacataccgtggttggg
3001 to 3075
                GsuI
                                                               BanI
                                                               Eco64I
```

FIG. 14-21

```
                                      ErhI
                                      StyI Eco130I
 BstXI           AlwNI                EcoT14I
cctggacggacagaagctggaccccaggatactcctaggtgatgactctcaaaagtttttttcctcattaccttg
base pairs
ggacctgcctgtcttcgacctggggtcctatgaggatccactactgagagttttcaaaaaaaggagtaatggaac
3076 to 3150
                                      BssT1I
                                      AvrII
                                      BlnI


                                                    BsaWI        BsgI
tggtggacttggggtggacagtgacaccatttggaatgagctacactcgtccggtgctgcacgcatggctgttgg
base pairs
accacctgaaccccacctgtcactgtggtaaaccttactcgatgtgagcaggccacgacgtgcgtaccgacaacc
3151 to 3225
```

FIG. 14-22

```
                              CvnI
                              AocI                                      CfrI
                              Bsu36I          Eco57I              DraII  EaeI
ctgtgtcatcgagctggcttccaaagtggcctcaggagagctgaagaatgggtttgctgttgtgaggccccctgg
base pairs
gacacagtagctcgaccgaaggtttcaccggagtcctctcgacttcttacccaaacgacaacactccgggggacc
3226 to 3300

                              Eco81I
                              Bse21I                             EcoO109I


MscI
                        ErhI Eco130I
                        BssT1I BstXI
                Eco57I  MslI DsaI
ccatcacgctgaagaatccacagccatggggttctgctttttaattcagttgcaattaccgccaaatacttgag
base pairs
ggtagtgcgacttcttaggtgtcggtaccccaagacgaaaaattaagtcaacgttaatggcggtttatgaactc
3301 to 3375
MluNI
BalI                    EcoT14I
                        StyI BstDSI
                        NcoI Bsp19I
```

FIG. 14-23

```
                                 BstX2I         NcoI Bsp19I Asp718I   SseBI
                                  BstYI         StyI BstDSI AccB1I
Eco147I
    BsaI                          XhoII         EcoT14I   BshNI       StuI
agaccaactaaatataagcaagatattgattgtagatctggatgttcaccatggaaacggtacccagcaggcctt
base pairs
tctggttgatttatattcgttctataactaacatctagacctacaagtggtacctttgccatgggtcgtccggaa
3376 to 3450
    Eco31I                        BglII         BssT1I    BanI KpnI   AatI
                                  MflI          ErhI Eco130I Eco64I   Pme55I
                                                DsaI      Acc65I

                     SspBI
                     Bsp1407I      MslI              Asp700I
ttatgctgaccccagcatcctgtacatttcactccatcgctatgatgaagggaactttttccctggcagtggagc
base pairs
aatacgactggggtcgtaggacatgtaaagtgaggtagcgatactacttcccttgaaaaagggaccgtcacctcg
3451 to 3525
                     BsrGI                           XmnI
```

FIG. 14-24

```
 FriOI                                FriOI                                     BstYI
 Eco24I                               Eco24I                                    XhoII
                                                                              BsrDI
cccaaatgaggttcggtttatttctttagagccccactttatttgtatctttcaggtaattgcattgca ggatc
base pairs
gggtttactccaagccaaataaagaaatctcggggtgaaataaacatagaaagtccattaacgtaacgt cctag
3526 to 3600
 BanII                                BanII
                                                                              BamHI
                                                                              BstI
                                                                              MflI

Acc65I
  BanI Eco64I                          AvaI BcoI
BstX2I Asp718I                       MflI Eco88I PspALI
                                     XhoII Cfr9I SmaI MslI
cggtaccagattacaaggacgacgatgacaagtagat cccgggtggcatccctgtgacccctccccagtgcctct
base pairs
gccatggtctaatgttcctgctgctactgttcatcta gggcccaccgtagggacactggggaggggtcacggaga
3601 to 3675
  BshNI                              BstYI Ama87I
 BsaWI KpnI                          BstX2I BsoBI
  AccB1I                                 XmaI PspAI
```

FIG. 14-25

```
     Eco130I
     StyI              GsuI
     EcoT14I          MslI
cctggccttggaagttgccactccagtgcccaccagccttgtcctaataaattaagttgcatcattttgtctga
base pairs
ggaccggaaccttcaacggtgaggtcacgggtggtcggaacaggattatttaattcaacgtagtaaaacagact
3676 to 3750
     BssT1I            BpmI
     ErhI

                                                       Eco24I
                                                                   SfcI
    Eam1105I                                        DraII BanII    Bbv16II
    AspEI       SspI                                PspOMI FriOI   BbsI
ctaggtgtcctctataatattatggggtggagggggtggtatggagcaaggggcccaagttggaagacaacct
base pairs
gatccacaggagatattataataccccacctcccccaccatacctcgttccccgggttcaacccttctgttgga
3751 to 3825
    EclHKI                                          Bsp120I        BpiI
    AhdI                                            EcoO109I       BpuAI
                                                       ApaI        BstSFI
```

FIG. 14-26

```
    DraII                                           BpmI BsgI
gtagggcctgcggggtctattcgggaaccaagctggagtgcagtggcacaatcttggctcactgcaatctccgcc
base pairs
catcccggacgccccagataagcccttggttcgacctcacgtcaccgtgttagaaccgagtgacgttagaggcgg
3826 to 3900
    EcoO109I                                        GsuI
```

```
                                          BcoI                     NspI        BlpI
                                          Ama87I                   PaeI Mph1103I
                                 BcgI     AvaI                   Ppu10I EcoT22I
tcctgggttcaagcgattctcctgcctcagcctcccgagttgttgggattccaggcatgcatgaccaggctcagc
base pairs
aggacccaagttcgctaagaggacggagtcggagggctcaacaaccctaaggtccgtacgtactggtccgagtcg
3901 to 3975
                                          Eco88I                   BbuI Zsp2I CelII
                                          BsoBI                    SphI       Bsp172
                                                                     NsiI     Bpu11
```

FIG. 14-27

```
                                           MscI
                                           MluNI
                     Esp3I                EaeI          BsaI
taattttgtttttttggtagagacggggtttcaccatattggccaggctggtctccaactcctaatctcaggtg
base pairs
attaaaacaaaaaaaccatctctgccccaaagtggtataaccggtccgaccagaggttgaggattagagtccac
3976 to 4050
                     BsmBI                CfrI          Eco31I
 0I                                        BalI
02I

        Eco130I
        StyI
        EcoT14I         BstXI
atctacccaccttggcctcccaaattgctgggattacaggcgtgaaccactgctcccttccctgtccttctgatt
base pairs
tagatgggtggaaccggagggtttaacgaccctaatgtccgcacttggtgacgagggaagggacaggaagactaa
4051 to 4125
        BssT1I
        ErhI
```

FIG. 14-28

```
                        BbiII                          NcoI Eco130I BsrFI PflMI
                        HinlI                          StyI DsaI AgeI Bse118I
  DraI                  AcyI AatII                     EcoT14I   BsaWI AccB7I
ttaaaataactataccagcaggaggacgtccagacacagcataggctacctgccatggcccaaccggtgggacat
base pairs
aatttattgatatggtcgtcctcctgcaggtctgtgtcgtatccgatggacggtaccgggttggccaccctgta
4126 to 4200
                        Msp17I                         BssT1I    BssAI Esp1396I
                        BsaHI                          ErhI BstDSI PinAI Van91I
                        Hsp92I                         BspMI Bsp19I Cfr10I

                                                                         EaeI
ttgagttgcttgcttggcactgtcctctcatgcgttgggtccactcagtagatgcctgttgaattgggtacgcgg
base pairs
aactcaacgaacgaaccgtgacaggagagtacgcaacccaggtgagtcatctacggacaacttaacccatgcgcc
4201 to 4275
                                                                         CfrI
```

FIG. 14-29

```
       AlwNI
ccagcttctgtggaatgtgtgtcagttagggtgtggaaagtccccaggctccccagcaggcagaagtatgcaaag
base pairs
ggtcgaagacaccttacacacagtcaatcccacacctttcaggggtccgaggggtcgtccgtcttcatacgtttc
4276 to 4350


    NspI
    PaeI Mph1103I
  Ppu10I EcoT22I        SexAI
catgcatctcaattagtcagcaaccaggtgtggaaaagtccccaggctccccagcaggcagaagtatgcaaagca
base pairs
gtacgtagagttaatcagtcgttggtccacaccttttcaggggtccgaggggtcgtccgtcttcatacgtttcgt
4351 to 4425
    BbuI Zsp2I
    SphI
      NsiI
```

FIG. 14-30

```
  NspI
  PaeI Mph1103I
Ppu10I EcoT22I
tgcatctcaattagtcagcaaccatagtcccgcccctaactccgcccatcccgcccctaactccgcccagttccg
base pairs
acgtagagttaatcagtcgttggtatcagggcggggattgaggcgggtagggcggggattgaggcgggtcaaggc
4426 to 4500
  BbuI Zsp2I
  SphI
    NsiI

              NcoI Bsp19I
              StyI BstDSI
              EcoT14I                                   BglI
cccattctccgccccatggctgactaatttttttatttatgcagaggccgaggccgcctcggcctctgagctat
base pairs
gggtaagaggcggggtaccgactgattaaaaaaataaatacgtctccggctccggcggagccggagactcgata
4501 to 4575
              BssT1I                                    SfiI
              ErhI Eco130I
              DsaI
```

FIG. 14-31

```
                              SseBI AvrII             Ama87I
                              Eco147I BlnI            Eco88I BseRI
                 BseRI        StuI BssT1I             AvaI BsoBI
tccagaagtagtgaggaggcttttttggaggcctaggcttttgcaaaaagctc ctcgaggaactgaaaaaccaga
base pairs
aggtcttcatcactcctccgaaaaaacctccggatccgaaaacgtttttcgag gagctccttgactttttggtct
4576 to 4650
                              AatI StyI               XhoI BcoI
                              Pme55I ErhI             Sfr274I
                               EcoT14I Eco130I        PaeR7I


          SfcI          ApoI
aagttaattccctatagtgagtcgtattaaattcgtaatcatggtcatagctgtttcctgtgtgaaattgttatc
base pairs
ttcaattaagggatatcactcagcataatttaagcattagtaccagtatcgacaaaggacacactttaacaatag
4651 to 4725
          BstSFI        AcsI
```

FIG. 14-32

```
     AccBSI                                                AccB1I
     BsrBI                                                 BshNI
cgctcacaattccacacaacatacgagccggaagcataaagtgtaaagcctggggtgcctaatgagtgagctaac
base pairs
gcgagtgttaaggtgtgttgtatgctcggccttcgtatttcacatttcggaccccacggattactcactcgattg
4726 to 4800
     BstD102I                                              BanI
                                                          Eco64I

                                                                 VspI
      VspI                                                 MspA1I
      PshBI                                                 PvuII  PshBI
                                                                       EaeI
tcacattaattgcgttgcgctcactgcccgctttccagtcgggaaacctgtcgtgccagctgcattaatgaatcg
base pairs
agtgtaattaacgcaacgcgagtgacgggcgaaaggtcagccctttggacagcacggtcgacgtaattacttagc
4801 to 4875
      AsnI                                                  NspBII
                                                                       CfrI
      AseI                                                       AsnI
                                                                 AseI
```

FIG. 14-33

```
                                          Eam1104I
                                      BstH2I
                                      Bsp143II
gccaacgcgcggggagaggcggtttgcgtattgggcgctcttccgcttcctcgctcactgactcgctgcgctcgg
base pairs
cggttgcgcgcccctctccgccaaacgcataacccgcgagaaggcgaaggagcgagtgactgagcgacgcgagcc
4876 to 4950
                                      HaeII EarI
                                          SapI
                                          Ksp632I

 BstMCI                AccBSI
 BsaOI                 BsrBI
tcgttcggctgcggcgagcggtatcagctcactcaaaggcggtaatacggttatccacagaatcaggggataacg
base pairs
agcaagccgacgccgctcgccatagtcgagtgagtttccgccattatgccaataggtgtcttagtcccctattgc
4951 to 5025
 Bsh1285I              BstD102I
 BsiEI
```

FIG. 14-34

```
          NspI
     BspLU11I
caggaaagaacatgtgagcaaaaggccagcaaaaggccaggaaccgtaaaaaggccgcgttgctggcgtttttcc
base pairs
gtcctttcttgtacactcgttttccggtcgttttccggtccttggcatttttccggcgcaacgaccgcaaaaagg
5026 to 5100
     AflIII

                                             DrdI
ataggctccgcccccctgacgagcatcacaaaaatcgacgctcaagtcagaggtggcgaaacccgacaggactat
base pairs
tatccgaggcggggggactgctcgtagtgtttttagctgcgagttcagtctccaccgctttgggctgtcctgata
5101 to 5175
```

FIG. 14-35

```
                                      BsiI                     BsaWI
aaagataccaggcgtttccccctggaagctccctcgtgcgctctcctgttccgaccctgccgcttaccggatacc
base pairs
tttctatggtccgcaaagggggaccttcgagggagcacgcgagaggacaaggctgggacggcgaatggcctatgg
5176 to 5250
                                      BssSI
```

```
                                 BstH2I
                                 Bsp143II      SfcI
tgtccgcctttctcccttcgggaagcgtggcgctttctcaatgctcacgctgtaggtatctcagttcggtgtagg
base pairs
acaggcggaaagagggaagcccttcgcaccgcgaaagagttacgagtgcgacatccatagagtcaagccacatcc
5251 to 5325
                                 HaeII         BstSFI
```

FIG. 14-36

```
               BsiHKAI                    NspBII
             Alw44I                      BstMCI
             VneI Bbv12I                 BsaOI       BsaWI
tcgttcgctccaagctgggctgtgtgcacgaaccccccgttcagcccgaccgctgcgccttatccggtaactatc
base pairs
agcaagcgaggttcgacccgacacacgtgcttggggggcaagtcgggctggcgacgcggaataggccattgatag
5326 to 5400
             ApaLI                       Bsh1285I
               AspHI                     BsiEI
               Alw21I                     MspA1I
```

```
                                          AlwNI
gtcttgagtccaacccggtaagacacgacttatcgccactggcagcagccactggtaacaggattagcagagcga
base pairs
cagaactcaggttgggccattctgtgctgaatagcggtgaccgtcgtcggtgaccattgtcctaatcgtctcgct
5401 to 5475
```

FIG. 14-37

```
                SfcI
ggtatgtaggcggtgctacagagttcttgaagtggtggcctaactacggctacactagaagaacagtatttggta
base pairs
ccatacatccgccacgatgtctcaagaacttcaccaccggattgatgccgatgtgatcttcttgtcataaaccat
5476 to 5550
                BstSFI
```

```
                Eco57I
                                                                      NspBII
tctgcgctctgctgaagccagttaccttcggaaaaagagttggtagctcttgatccggcaaacaaaccaccgctg
base pairs
agacgcgagacgacttcggtcaatggaagcctttttctcaaccatcgagaactaggccgtttgtttggtggcgac
5551 to 5625
                                                                      MspA1I
```

FIG. 14-38

```
                                                     MflI         MflI
                                                     XhoII        XhoII
gtagcggtggtttttttgtttgcaagcagcagattacgcgcagaaaaaaaggatctcaagaagatcctttgatct
base pairs
catcgccaccaaaaaaacaaacgttcgtcgtctaatgcgcgtctttttttcctagagttcttctaggaaactaga
5626 to 5700
                                                     BstYI        BstYI
                                                     BstX2I       BstX2I

                                                        RcaI             MflI
                                                                        XhoII
tttctacggggtctgacgctcagtggaacgaaaactcacgttaagggattttggtcatgagattatcaaaaagga
base pairs
aaagatgccccagactgcgagtcaccttgcttttgagtgcaattccctaaaaccagtactctaatagtttttcct
5701 to 5775
                                                        BspHI            BstYI
                                                                         BstX2I
```

FIG. 14-39

```
          MflI
          XhoII    DraI                   DraI
tcttcacctagatccttttaaattaaaaatgaagttttaaatcaatctaaagtatatatgagtaaacttggtctg
base pairs
agaagtggatctaggaaaatttaatttttacttcaaaatttagttagatttcatatatactcatttgaaccagac
5776 to 5850
          BstYI
          BstX2I

                        AccB1I
                        BshNI
acagttaccaatgcttaatcagtgaggcacctatctcagcgatctgtctatttcgttcatccatagttgcctgac
base pairs
tgtcaatggttacgaattagtcactccgtggatagagtcgctagacagataaagcaagtaggtatcaacggactg
5851 to 5925
                        BanI
                        Eco64I
```

FIG. 14-40

```
   Eam1105I
   AspEI                                                          BsrDI
tccccgtcgtgtagataactacgatacgggagggcttaccatctggccccagtgctgcaatgataccgcgagacc
base pairs
aggggcagcacatctattgatgctatgccctcccgaatggtagaccggggtcacgacgttactatggcgctctgg
5926 to 6000
   EclHKI
   AhdI


        Cfr10I
BsaI    BssAI     BpmI                         BglI
cacgctcaccggctccagatttatcagcaataaaccagccagccggaagggccgagcgcagaagtggtcctgcaa
base pairs
gtgcgagtggccgaggtctaaatagtcgttatttggtcggtcggccttcccggctcgcgtcttcaccaggacgtt
6001 to 6075
Eco31I  BsrFI     GsuI
        Bse118I
```

FIG. 14-41

```
                          VspI
                          PshBI
ctttatccgcctccatccagtctattaattgttgccgggaagctagagtaagtagttcgccagttaatagtttgc
base pairs
gaaataggcggaggtaggtcagataattaacaacggcccttcgatctcattcatcaagcggtcaattatcaaacg
6076 to 6150
                          AsnI
                          AseI

AviII               BstSFI
FspI                SfcI        MslI                                       BsaWI
gcaacgttgttgccattgctacaggcatcgtggtgtcacgctcgtcgtttggtatggcttcattcagctccggtt
base pairs
cgttgcaacaacggtaacgatgtccgtagcaccacagtgcgagcagcaaaccataccgaagtaagtcgaggccaa
6151 to 6225
Acc16I              BsrDI
    Psp1406I
```

FIG. 14-42

```
                                                             BsiEI
                                                              PvuI
                                                            BstMCI
                                                             BsaOI
cccaacgatcaaggcgagttacatgatcccccatgttgtgcaaaaaagcggttagctccttcggtcctccgatcg
base pairs
gggttgctagttccgctcaatgtactagggggtacaacacgttttttcgccaatcgaggaagccaggaggctagc
6226 to 6300

                                                             BspCI
                                                          Bsh1285I
                                                            Ple19I

             EaeI                 MslI
ttgtcagaagtaagttggccgcagtgttatcactcatggttatggcagcactgcataattctcttactgtcatgc
base pairs
aacagtcttcattcaaccggcgtcacaatagtgagtaccaataccgtcgtgacgtattaagagaatgacagtacg
6301 to 6375
             CfrI
```

FIG. 14-43

```
                         Acc113I
                                                                   BstMCI
                         Eco255I                                   BsaOI
catccgtaagatgcttttctgtgactggtgagtactcaaccaagtcattctgagaatagtgtatgcggcgaccga
base pairs
gtaggcattctacgaaaagacactgaccactcatgagttggttcagtaagactcttatcacatacgccgctggct
6376 to 6450
                         ScaI
                                                                  Bsh1285I
                                                                   BsiEI

              BbiII
              Hin1I                                         Alw21I
     BcgI     AcyI                                   DraI   AspHI
gttgctcttgcccggcgtcaatacgggataataccgcgccacatagcagaactttaaaagtgctcatcattggaa
base pairs
caacgagaacgggccgcagttatgccctattatggcgcggtgtatcgtcttgaaattttcacgagtagtaacctt
6451 to 6525
              Msp17I                                        BsiHKAI
              BsaHI                                         Bbv12I
              Hsp92I
```

FIG. 14-44

```
                                                                        BsssI
  XmnI                        MflI              MflI                  Alw44I
  Psp1406I                    XhoII      NspBII XhoII                 VneI
aacgttcttcggggcgaaaactctcaaggatcttaccgctgttgagatccagttcgatgtaacccactcgtgcac
base pairs
ttgcaagaagccccgcttttgagagttcctagaatggcgacaactctaggtcaagctacattgggtgagcacgtg
6526 to 6600
  Asp700I                     BstYI      MspA1I BstYI                 ApaLI
                             BstX2I             BstX2I                 BsiI
                                                                      AspHI


  Bbv12I
BsiHKAI        Eco57I
ccaactgatcttcagcatcttttactttcaccagcgtttctgggtgagcaaaaacaggaaggcaaaatgccgcaa
base pairs
ggttgactagaagtcgtagaaaatgaaagtggtcgcaaagacccactcgtttttgtccttccgttttacggcgtt
6601 to 6675
 Alw21I
```

FIG. 14-45

```
                                                    EarI
                      MslI                          Eam1104I   SspI
aaaagggaataagggcgacacggaaatgttgaatactcatactcttcctttttcaatattattgaagcatttatc
base pairs
ttttcccttattcccgctgtgcctttacaacttatgagtatgagaaggaaaaagttataataacttcgtaaatag
6676 to 6750
                                                    Ksp632I
```

```
                          AccBSI
             RcaI         BsrBI
agggttattgtctcatgagcggatacatatttgaatgtatttagaaaaataaacaaataggggttccgcgcacat
base pairs
tcccaataacagagtactcgcctatgtataaacttacataaatctttttatttgtttatccccaaggcgcgtgta
6751 to 6825
             BspHI        BstD102I
```

FIG. 14-46

```
                               SfcI
ttccccgaaaagtgccacctgacgcgccctgtagcggcgcattaagcgcggcgggtgtggtggttacgcgcagcg
base pairs
aaggggcttttcacggtggactgcgcgggacatcgccgcgtaattcgcgccgcccacaccaccaatgcgcgtcgc
6826 to 6900
                               BstSFI
```

```
                                    AccBSI                              BsrFI
                  BstH2I    HaeII   BstD102I                            BssAI
                  Bsp143II          BsrBI                               MroNI
tgaccgctacacttgccagcgccctagcgcccgctcctttcgctttcttcccttcctttctcgccacgttcgccg
base pairs
actggcgatgtgaacggtcgcgggatcgcgggcgaggaaagcgaaagaagggaaggaaagagcggtgcaagcggc
6901 to 6975
                  HaeII     Bsp143II                                    NgoAIV
                                                                        NgoMI
                            BstH2I                                      Bse118I
```

FIG. 14-47

NaeI AccB1I BshNI

gctttccccgtcaagctctaaatcggggcatccctttagggttccgatttagtgctttacggcacctcgacccca
base pairs
cgaaaggggcagttcgagatttagccccgtagggaaatcccaaggctaaatcacgaaatgccgtggagctggggt
6976 to 7050

Cfr10I BanI Eco64I

BsaAI DrdI

aaaaacttgattagggtgatggttcacgtagtgggccatcgccctgatagacggtttttcgccctttgacgttgg
base pairs
tttttgaactaatcccactaccaagtgcatcacccggtagcgggactatctgccaaaaagcgggaaactgcaacc
7051 to 7125

DraIII

FIG. 14-48

```
agtccacgttctttaatagtggactcttgttccaaactggaacaacactcaaccctatctcggtctattctttg
base pairs
tcaggtgcaagaaattatcacctgagaacaaggtttgaccttgttgtgagttgggatagagccagataagaaac
7126 to 7200

                                                                 ApoI       ApoI
atttataagggattttgccgatttcggcctattggttaaaaaatgagctgatttaacaaaaatttaacgcgaatt
base pairs
taaatattccctaaaacggctaaagccggataaccaattttttactcgactaaattgtttttaaattgcgcttaa
7201 to 7275
                                                                 AcsI       AcsI

         SspI  Psp1406I
ttaacaaaatattaaacgtttacaattt  base pairs
aattgttttataatttgcaaatgttaaa  7276 to 7303
```

FIG. 14-49

Table by Enzyme Name

Enzyme name	No. cuts	Positions of sites	Recognition sequence	
AatI	2	3446 4606	agg/cct	More info
AatII	5	451 504 587 773 4154	gacgt/c	More info
Acc113I	1	6408	agt/act	More info
Acc16I	2	21 6150	tgc/gca	More info
Acc65I	3	2264 3434 3602	g/ gtacc	More info
AccB1I	8	791 2264 3065 3434 3602 4779 5876 7036	g/ gyrcc	More info
AccB7I	6	1445 1482 1775 1796 2644 4191	ccannnn/ntgg	More info
AccBSI	4	4730 4971 6772 6936	gagcgg	More info
AclNI	1	326	a/ ctagt	More info
AcsI	7	912 1990 2244 2994 4679 7260 7271	r/ aatty	More info
AcyI	6	448 501 584 770 4151 6465	gr/cgyc	More info
AflIII	2	2702 5035	a/ crygt	More info
AgeI	1	4188	a/ ccggt	More info
AhdI	2	3754 5928	gacnnn/nngtc	More info
Alw21I	6	894 1576 2330 5353 6514 6599	gwgcw/c	More info
Alw44I	2	5349 6595	g/ tgcac	More info

FIG. 14-50

AlwNI	6	1147 1273 1775 3091 4282 5451	cagnnn/ctg	More info
Ama87I	3	3638 3934 4629	c/ ycgrg	More info
AocI	3	1034 1046 3256	cc/ tnagg	More info
ApaI	1	3806	gggcc/c	More info
ApaLI	2	5349 6595	g/ tgcac	More info
ApoI	7	912 1990 2244 2994 4679 7260 7271	r/ aatty	More info
AseI	4	334 4806 4865 6100	at/ taat	More info
AsnI	4	334 4806 4865 6100	at/ taat	More info
Asp700I	4	1107 2481 3506 6527	gaann/nnttc	More info
Asp718I	3	2264 3434 3602	g/ gtacc	More info
AspEI	2	3754 5928	gacnnn/nngtc	More info
AspHI	6	894 1576 2330 5353 6514 6599	gwgcw/c	More info
AvaI	3	3638 3934 4629	c/ ycgrg	More info
AviII	2	21 6150	tgc/gca	More info
AvrII	2	3109 4607	c/ ctagg	More info
BalI	4	184 238 3300 4018	tgg/cca	More info
BamHI	1	3596	g/ gatcc	More info
BanI	8	791 2264 3065 3434 3602 4779 5876 7036	g/ gyrcc	More info
BanII	6	894 1017 1623 3526 3558 3806	grgcy/c	More info
BanIII	1	939	at/ cgat	More info
BbiII	6	448 501 584 770 4151 6465	gr/cgyc	More info

FIG. 14-51

BbrPI	1	2705	cac/gtg	More info
BbsI	2	2512 3820	gaagac	More info
BbuI	4	2930 3959 4354 4427	gcatg/c	More info
Bbv12I	6	894 1576 2330 5353 6514 6599	gwgcw/c	More info
Bbv16II	2	2512 3820	gaagac	More info
BcgI	4	941 2556 3925 6455	cgannnnnntgc	More info
BclI	1	969	t/ gatca	More info
BcoI	3	3638 3934 4629	c/ ycgrg	More info
BglI	5	14 417 538 4560 6048	gccnnnn/nggc	More info
BglII	2	932 3409	a/ gatct	More info
BlnI	2	3109 4607	c/ ctagg	More info
BlpI	3	1200 2337 3970	gc/tnagc	More info
BpiI	2	2512 3820	gaagac	More info
BpmI	9	1015 1279 1772 2781 2842 3022 3701 3863 6018	ctggag	More info
Bpu1102I	3	1200 2337 3970	gc/tnagc	More info
Bpu14I	3	1603 1988 2423	tt/cgaa	More info
BpuAI	2	2512 3820	gaagac	More info
Bsa29I	1	939	at/ cgat	More info
BsaAI	3	666 2705 7077	yac/gtr	More info
BsaHI	6	448 501 584 770 4151 6465	gr/cgyc	More info

FIG. 14-52

BsaI	3	3380 4031 6000	ggtctc	More info
BsaMI	1	1886	gaatgc	More info
BsaOI	7	42 424 928 4951 5375 6298 6447	cgry/cg	More info
BsaWI	6	3200 3599 4188 5241 5388 6219	w/ ccggw	More info
BscI	1	939	at/ cgat	More info
Bse118I	3	4188 6008 6972	r/ ccggy	More info
Bse21I	3	1034 1046 3256	cc/ tnagg	More info
BseCI	1	939	at/ cgat	More info
BseRI	4	1337 1671 4593 4631	gaggag	More info
BsgI	3	2315 3212 3868	gtgcag	More info
Bsh1285I	7	42 424 928 4951 5375 6298 6447	cgry/cg	More info
BshNI	8	791 2264 3065 3434 3602 4779 5876 7036	g/ gyrcc	More info
BsiEI	7	42 424 928 4951 5375 6298 6447	cgry/cg	More info
BsiHKAI	6	894 1576 2330 5353 6514 6599	gwgcw/c	More info
BsiI	2	5213 6597	ctcgtg	More info
BsmBI	3	2023 2773 4001	cgtctc	More info
BsmI	1	1886	gaatgc	More info
BsoBI	3	3638 3934 4629	c/ ycgrg	More info
Bsp106I	1	939	at/ cgat	More info
Bsp119I	3	1603 1988 2423	tt/cgaa	More info
Bsp120I	1	3802	g/ ggccc	More info
Bsp1407I	2	270 3471	t/ gtaca	More info

FIG. 14-53

Bsp143II	5	2519 4913 5283 6922 6930	rgcgc/y	More info
Bsp1720I	3	1200 2337 3970	gc/tnagc	More info
Bsp19I	5	686 3324 3424 4178 4514	c/ catgg	More info
BspCI	2	42 6298	cgat/cg	More info
BspDI	1	939	at/ cgat	More info
BspHI	3	1891 5755 6763	t/ catga	More info
BspLU11I	1	5035	a/ catgt	More info
BspMI	2	1913 4178	acctgc	More info
BspXI	1	939	at/ cgat	More info
BsrBI	4	4730 4971 6772 6936	gagcgg	More info
BsrDI	5	245 2827 3594 5987 6169	gcaatg	More info
BsrFI	3	4188 6008 6972	r/ ccggy	More info
BsrGI	2	270 3471	t/ gtaca	More info
BssAI	3	4188 6008 6972	r/ ccggy	More info
BssSI	2	5213 6597	ctcgtg	More info
BssT1I	11	686 1950 2226 3109 3324 3424 3681 4060 4178 4514 4607	c/ cwwgg	More info
BstBI	3	1603 1988 2423	tt/cgaa	More info
BstD102I	4	4730 4971 6772 6936	gagcgg	More info
BstDSI	6	686 1062 3324 3424 4178 4514	c/ crygg	More info
BstH2I	5	2519 4913 5283 6922 6930	rgcgc/y	More info
BstI	1	3596	g/ gatcc	More info

FIG. 14-54

BstMCI	7	42 424 928 4951 5375 6298 6447	cgry/cg	More info
BstSFI	8	944 2144 3824 4662 5300 5491 6169 6854	c/ tryag	More info
BstSNI	1	666	tac/gta	More info
BstX2I	12	932 2400 2634 3409 3596 3634 5676 5687 5773 5785 6553 6570	r/ gatcy	More info
BstXI	3	3076 3325 4077	ccannnnn/ntgg	More info
BstYI	12	932 2400 2634 3409 3596 3634 5676 5687 5773 5785 6553 6570	r/ gatcy	More info
BstZI	1	925	c/ ggccg	More info
Bsu15I	1	939	at/ cgat	More info
Bsu36I	3	1034 1046 3256	cc/ tnagg	More info
CciNI	1	925	gc/ggccgc	More info
CelII	3	1200 2337 3970	gc/tnagc	More info
Cfr10I	3	4188 6008 6972	r/ ccggy	More info
Cfr9I	1	3638	c/ ccggg	More info
CfrI	9	152 182 236 925 3298 4016 4273 4874 6316	y/ ggccr	More info
ClaI	1	939	at/ cgat	More info
Csp45I	3	1603 1988 2423	tt/cgaa	More info
CvnI	3	1034 1046 3256	cc/ tnagg	More info

FIG. 14-55

DraI	4	4127 5794 5813 6505	ttt/aaa	More info
DraII	3	3291 3802 3829	rg/gnccy	More info
DraIII	1	7080	cacnnn/gtg	More info
DrdI	3	1076 5143 7124	gacnnnn/nngtc	More info
DsaI	6	686 1062 3324 3424 4178 4514	c/ crygg	More info
EaeI	9	152 182 236 925 3298 4016 4273 4874 6316	y/ ggccr	More info
EagI	1	925	c/ ggccg	More info
Eam1104I	5	58 2482 2793 4918 6722	ctcttc	More info
Eam1105I	2	3754 5928	gacnnn/nngtc	More info
EarI	5	58 2482 2793 4918 6722	ctcttc	More info
Ecl136II	1	892	gag/ ctc	More info
EclHKI	2	3754 5928	gacnnn/nngtc	More info
EclXI	1	925	c/ ggccg	More info
Eco105I	1	666	tac/gta	More info
Eco130I	11	686 1950 2226 3109 3324 3424 3681 4060 4178 4514 4607	c/ cwwgg	More info
Eco147I	2	3446 4606	agg/cct	More info
Eco24I	6	894 1017 1623 3526 3558 3806	grgcy/c	More info
Eco255I	1	6408	agt/act	More info
Eco31I	3	3380 4031 6000	ggtctc	More info
Eco32I	1	952	gat/ atc	More info
Eco52I	1	925	c/ ggccg	More info

FIG. 14-56

Eco57I	7	1210 2446 2488 3271 3314 5567 6615	ctgaag	More info
Eco64I	8	791 2264 3065 3434 3602 4779 5876 7036	g/ gyrcc	More info
Eco72I	1	2705	cac/gtg	More info
Eco81I	3	1034 1046 3256	cc/ tnagg	More info
Eco88I	3	3638 3934 4629	c/ ycgrg	More info
EcoICRI	1	892	gag/ ctc	More info
EcoNI	3	1259 1338 1684	cctnn/nnnagg	More info
EcoO109I	3	3291 3802 3829	rg/gnccy	More info
EcoRI	3	912 1990 2994	g/ aattc	More info
EcoRV	1	952	gat/ atc	More info
EcoT14I	11	686 1950 2226 3109 3324 3424 3681 4060 4178 4514 4607	c/ cwwgg	More info
EcoT22I	3	3961 4356 4429	atgca/t	More info
ErhI	11	686 1950 2226 3109 3324 3424 3681 4060 4178 4514 4607	c/ cwwgg	More info
Esp1396I	6	1445 1482 1775 1796 2644 4191	ccannnn/ntgg	More info
Esp3I	3	2023 2773 4001	cgtctc	More info
FauNDI	1	560	ca/ tatg	More info
FbaI	1	969	t/ gatca	More info
FriOI	6	894 1017 1623 3526 3558 3806	grgcy/c	More info
FspI	2	21 6150	tgc/gca	More info

FIG. 14-57

GsuI	9	1015 1279 1772 2781 2842 3022 3701 3863 6018	ctggag	More info
HaeII	5	2519 4913 5283 6922 6930	rgcgc/y	More info
Hin1I	6	448 501 584 770 4151 6465	gr/cgyc	More info
HincII	3	311 446 842	gty/rac	More info
HindII	3	311 446 842	gty/rac	More info
HindIII	3	918 1394 2183	a/ agctt	More info
Hsp92I	6	448 501 584 770 4151 6465	gr/cgyc	More info
KpnI	3	2268 3438 3606	ggtac/c	More info
Ksp22I	1	969	t/ gatca	More info
Ksp632I	5	58 2482 2793 4918 6722	ctcttc	More info
LspI	3	1603 1988 2423	tt/cgaa	More info
MfeI	1	1091	c/ aattg	More info
MflI	12	932 2400 2634 3409 3596 3634 5676 5687 5773 5785 6553 6570	r/ gatcy	More info
MluNI	4	184 238 3300 4018	tgg/cca	More info
Mph1103I	3	3961 4356 4429	atgca/t	More info
MroNI	1	6972	g/ ccggc	More info
MscI	4	184 238 3300 4018	tgg/cca	More info
MslI	10	691 2094 2703 3323 3489 3651 3698 6180 6339 6698	caynn/nnrtg	More info
Msp17I	6	448 501 584 770 4151 6465	gr/cgyc	More info
MspA1I	7	71 2341 2731 4859 5377 5622 6563	cmg/ckg	More info

FIG. 14-58

MunI	1	1091	c/ aattg	More info
Mva1269I	1	1886	gaatgc	More info
NaeI	1	6974	gcc/ggc	More info
NcoI	5	686 3324 3424 4178 4514	c/ catgg	More info
NdeI	1	560	ca/ tatg	More info
NgoAIV	1	6972	g/ ccggc	More info
NgoMI	1	6972	g/ ccggc	More info
NotI	1	925	gc/ggccgc	More info
NsiI	3	3961 4356 4429	atgca/t	More info
NspBII	7	71 2341 2731 4859 5377 5622 6563	cmg/ckg	More info
NspI	5	2930 3959 4354 4427 5039	rcatg/y	More info
NspV	3	1603 1988 2423	tt/cgaa	More info
PaeI	4	2930 3959 4354 4427	gcatg/c	More info
PaeR7I	1	4629	c/ tcgag	More info
PflMI	6	1445 1482 1775 1796 2644 4191	ccannnn/ntgg	More info
PinAI	1	4188	a/ ccggt	More info
Ple19I	2	42 6298	cgat/cg	More info
PmaCI	1	2705	cac/gtg	More info
Pme55I	2	3446 4606	agg/cct	More info
PmlI	1	2705	cac/gtg	More info
Ppu10I	3	3957 4352 4425	a/ tgcat	More info
PshBI	4	334 4806 4865 6100	at/ taat	More info
Psp124BI	1	894	gagct/c	More info
Psp1406I	3	6154 6527 7291	aa/cgtt	More info

FIG. 14-59

PspAI	1	3638	c/ ccggg	More info
PspALI	1	3640	ccc/ggg	More info
PspOMI	1	3802	g/ ggccc	More info
PstI	2	948 2148	ctgca/g	More info
PvuI	2	42 6298	cgat/cg	More info
PvuII	3	71 2341 4859	cag/ctg	More info
RcaI	3	1891 5755 6763	t/ catga	More info
SacI	1	894	gagct/c	More info
SapI	2	2483 4918	gctcttc	More info
ScaI	1	6408	agt/act	More info
SexAI	1	4373	a/ ccwggt	More info
SfcI	8	944 2144 3824 4662 5300 5491 6169 6854	c/ tryag	More info
SfiI	1	4560	ggccnnnn/nggcc	More info
Sfr274I	1	4629	c/ tcgag	More info
SfuI	3	1603 1988 2423	tt/cgaa	More info
SmaI	1	3640	ccc/ggg	More info
SnaBI	1	666	tac/gta	More info
SpeI	1	326	a/ ctagt	More info
SphI	4	2930 3959 4354 4427	gcatg/c	More info
SseBI	2	3446 4606	agg/cct	More info
SspBI	2	270 3471	t/ gtaca	More info
SspI	5	179 226 3768 6732 7285	aat/att	More info
SstI	1	894	gagct/c	More info

FIG. 14-60

StuI	2	3446 4606	agg/cct	More info
StyI	11	686 1950 2226 3109 3324 3424 3681 4060 4178 4514 4607	c/ cwwgg	More info
Van91I	6	1445 1482 1775 1796 2644 4191	ccannnn/ntgg	More info
VneI	2	5349 6595	g/ tgcac	More info
VspI	4	334 4806 4865 6100	at/ taat	More info
XcmI	2	1948 2897	ccannnnn/nnnntgg	More info
XhoI	1	4629	c/ tcgag	More info
XhoII	12	932 2400 2634 3409 3596 3634 5676 5687 5773 5785 6553 6570	r/gatcy	More info
XmaI	1	3638	c/ ccggg	More info
XmaIII	1	925	c/ ggccg	More info
XmnI	4	1107 2481 3506 6527	gaann/nnttc	More info
Zsp2I	3	3961 4356 4429	atgca/t	More info

The following endonucleases were selected but don't cut this sequence:
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FIG. 14-61

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Zhou, Xianbo
Rifkind, Richard A.
Marks, Paul A.

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            20                  25                  30
Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
        35                  40                  45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
    50                  55                  60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65                  70                  75                  80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
                85                  90                  95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
            100                 105                 110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
        115                 120                 125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
    130                 135                 140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145                 150                 155                 160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
                165                 170                 175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
            180                 185                 190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
        195                 200                 205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
    210                 215                 220
Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
225                 230                 235                 240
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Pro Leu Leu Arg Arg Lys Asp Gly Asn Val Val Thr Ser Phe Lys Lys
                245                 250                 255
Arg Met Phe Glu Val Thr Glu Ser Ser Val Ser Ser Ser Ser Pro Gly
            260                 265                 270
Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly Ser Val Thr Glu
        275                 280                 285
Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala Glu Gln Met Val
    290                 295                 300
Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met Asn Leu Leu Ser
305                 310                 315                 320
Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu Gly Leu Pro Ala
                325                 330                 335
Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys
            340                 345                 350
Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr
        355                 360                 365
Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His Val Thr Leu Glu
    370                 375                 380
Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu
385                 390                 395                 400
Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val Ala Gly Gly Val
                405                 410                 415
Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu Arg Ile Ser Pro
            420                 425                 430
Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg Pro Leu Asn Arg
        435                 440                 445
Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala Gln Leu Val Ile
    450                 455                 460
Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys Gln Tyr Gln Gln
465                 470                 475                 480
Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile Glu Gln Leu Lys
                485                 490                 495
Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu Leu Gln Gly Asp
            500                 505                 510
Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly Asn Ser Thr Arg
        515                 520                 525
Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly Gln Val Gly Ala
    530                 535                 540
Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile
545                 550                 555                 560
Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met Gln Gln Pro Phe
                565                 570                 575
Leu Glu Pro Thr His Thr Arg Ala Leu Ser Val Arg Gln Ala Pro Leu
            580                 585                 590
Ala Ala Val Gly Met Asp Gly Leu Glu Lys His Arg Leu Val Ser Arg
        595                 600                 605
Thr His Ser Ser Pro Ala Ala Ser Val Leu Pro His Pro Ala Met Asp
    610                 615                 620
Arg Pro Leu Gln Pro Gly Ser Ala Thr Gly Ile Ala Tyr Asp Pro Leu
625                 630                 635                 640
Met Leu Lys His Gln Cys Val Cys Gly Asn Ser Thr Thr His Pro Glu
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His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg Leu Gln Glu Thr Gly
            660                 665                 670
Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys Ala Ser Leu Glu
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Glu Ile Gln Leu Val His Ser Glu His His Ser Leu Leu Tyr Gly Thr
    690                 695                 700
Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile Leu Leu Gly Asp
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        755                 760                 765
Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro Gly His His Ala
    770                 775                 780
Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn Ser Val Ala Ile
785                 790                 795                 800
Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser Lys Ile Leu Ile
                805                 810                 815
Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln Gln Ala Phe Tyr
            820                 825                 830
Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg Tyr Asp Glu Gly
        835                 840                 845
Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val Gly Thr Gly Leu
    850                 855                 860
Gly Glu Gly Tyr Asn Ile Asn Ile Ala Trp Thr Gly Gly Leu Asp Pro
865                 870                 875                 880
Pro Met Gly Asp Val Glu Tyr Leu Glu Ala Phe Arg Thr Ile Val Lys
                885                 890                 895
Pro Val Ala Lys Glu Phe Asp Pro Asp Met Val Leu Val Ser Ala Gly
            900                 905                 910
Phe Asp Ala Leu Glu Gly His Thr Pro Pro Leu Gly Gly Tyr Lys Val
        915                 920                 925
Thr Ala Lys Cys Phe Gly His Leu Thr Lys Gln Leu Met Thr Leu Ala
    930                 935                 940
Asp Gly Arg Val Val Leu Ala Leu Glu Gly Gly His Asp Leu Thr Ala
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Ile Cys Asp Ala Ser Glu Ala Cys Val Asn Ala Leu Leu Gly Asn Glu
                965                 970                 975
Leu Glu Pro Leu Ala Glu Asp Ile Leu His Gln Ser Pro Asn Met Asn
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Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
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Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
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Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
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Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
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Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
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Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
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Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
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Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
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Arg Met Phe Glu Val Thr Glu Ser Ser Val Ser Ser Ser Ser Pro Gly
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325 330 335
Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys
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Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr
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Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu
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Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile
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Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met Gln Gln Pro Phe
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Glu Ile Gln Leu Val His Ser Glu His His Ser Leu Leu Tyr Gly Thr
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Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser Gly Ala Ala Arg
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Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys Val Ala Ser Gly
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Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro Gly His His Ala
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Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn Ser Val Ala Ile
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Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser Lys Ile Leu Ile
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Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln Gln Ala Phe Tyr
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Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg Tyr Asp Glu Gly
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Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val Arg Phe Ile Ser
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<212> DNA
<213> Homo sapiens

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<212> PRT
<213> Homo sapiens

<400> 6

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        35                  40                  45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
    50                  55                  60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65                  70                  75                  80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
                85                  90                  95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
            100                 105                 110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
        115                 120                 125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
    130                 135                 140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145                 150                 155                 160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
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Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
            180                 185                 190
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Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
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Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
225                 230                 235                 240
Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
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Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
            260                 265                 270
Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
        275                 280                 285
Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
    290                 295                 300
Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
305                 310                 315                 320
Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
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Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
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Gln His Leu Leu Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val
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Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
    370                 375                 380
Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
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Pro Leu Asn Arg Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala
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Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
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Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
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Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
            500                 505                 510
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Gln Gln Pro Phe Leu Glu Pro Thr His Thr Arg Ala Leu Ser Val Arg
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Leu Val Ser Arg Thr His Ser Ser Pro Ala Ala Ser Val Leu Pro His
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Pro Ala Met Asp Arg Pro Leu Gln Pro Gly Ser Ala Thr Gly Ile Ala
            580                 585                 590
Tyr Asp Pro Leu Met Leu Lys His Gln Cys Val Cys Gly Asn Ser Thr
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Thr His Pro Glu His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg Leu
    610                 615                 620
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Ala Ser Leu Glu Glu Ile Gln Leu Val His Ser Glu His His Ser Leu
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Leu Tyr Gly Thr Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile
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Leu Leu Gly Asp Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly
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Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
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Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
            740                 745                 750
Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
        755                 760                 765
Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
    770                 775                 780
Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
785                 790                 795                 800
Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
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Gly Thr Gly Leu Gly Glu Gly Tyr Asn Ile Asn Ile Ala Trp Thr Gly
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Gly Leu Asp Pro Pro Met Gly Asp Val Glu Tyr Leu Glu Ala Phe Arg
        835                 840                 845
Thr Ile Val Lys Pro Val Ala Lys Glu Phe Asp Pro Asp Met Val Leu
    850                 855                 860
Val Ser Ala Gly Phe Asp Ala Leu Glu Gly His Thr Pro Pro Leu Gly
865                 870                 875                 880
Gly Tyr Lys Val Thr Ala Lys Cys Phe Gly His Leu Thr Lys Gln Leu
                885                 890                 895
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Asp Leu Thr Ala Ile Cys Asp Ala Ser Glu Ala Cys Val Asn Ala Leu
        915                 920                 925
Leu Gly Asn Glu Leu Glu Pro Leu Ala Glu Asp Ile Leu His Gln Ser
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<211> 3367
<212> DNA
<213> Homo sapiens

<400> 7

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cagaagcaat accagcagca gatccacatg aacaaactgc tttcgaaatc tattgaacaa 1500
ctgaagcaac caggcagtca ccttgaggaa gcagaggaag agcttcaggg ggaccaggcg 1560
atgcaggaag acagagcgcc ctctagtggc aacagcacta ggagcgacag cagtgcttgt 1620
gtggatgaca cactgggaca agttggggct gtgaaggtca aggaggaacc agtggacagt 1680
gatgaagatg ctcagatcca ggaaatggaa tctggggagc aggctgcttt tatgcaacag 1740
cctttcctgg aacccacgca cacacgtgcg ctctctgtgc gccaagctcc gctggctgcg 1800
gttggcatgg atggattaga gaaacaccgt ctcgtctcca ggactcactc ttcccctgct 1860
gcctctgttt tacctcaccc agcaatggac cgcccccctcc agcctggctc tgcaactgga 1920
attgcctatg acccccttgat gctgaaacac cagtgcgttt gtggcaattc caccacccac 1980
cctgagcatg ctggacgaat acagagtatc tggtcacgac tgcaagaaac tgggctgcta 2040
aataaatgtg agcgaattca aggtcgaaaa gccagcctgg aggaaataca gcttgttcat 2100
tctgaacatc actcactgtt gtatggcacc aacccccctgg acggacagaa gctggacccc 2160
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ggggtggaca gtgacaccat ttggaatgag ctacactcgt ccggtgctgc acgcatggct 2280
gttggctgtg tcatcgagct ggcttccaaa gtggcctcag gagagctgaa gaatgggttt 2340
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ccaccgtggt gtgtctttct cttcccaggt tggaacaggc cttggagaag ggtacaatat 2940
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attcaggacc atcgtgaagc ctgtggccaa agagtttgat ccagacatgg tcttagtatc 3060
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aaaatgtttt ggtcatttga cgaagcaatt gatgacattg gctgatggac gtgtggtgtt 3180
ggctctagaa ggaggacatg atctcacagc catctgtgat gcatcagaag cctgtgtaaa 3240
tgcccttcta ggaaatgagc tggagccact tgcagaagat attctccacc aaagcccgaa 3300
tatgaatgct gttatttctt tacagaagat cattgaaatt caaagtatgt ctttaaagtt 3360
ctcttaa 3367

<210> 8
<211> 835
<212> PRT
<213> Homo sapiens

<400> 8
Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
1 5 10 15
Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
20 25 30
Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
35 40 45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50 55 60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65 70 75 80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85 90 95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100 105 110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115 120 125

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Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
    130                 135                 140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145                 150                 155                 160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
                165                 170                 175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
            180                 185                 190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
        195                 200                 205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
    210                 215                 220
Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
225                 230                 235                 240
Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
                245                 250                 255
Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
            260                 265                 270
Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
        275                 280                 285
Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
    290                 295                 300
Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
305                 310                 315                 320
Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
                325                 330                 335
Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
            340                 345                 350
Gln His Leu Leu Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val
        355                 360                 365
Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
    370                 375                 380
Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
385                 390                 395                 400
Pro Leu Asn Arg Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala
                405                 410                 415
Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
            420                 425                 430
Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
        435                 440                 445
Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
    450                 455                 460
Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
465                 470                 475                 480
Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
                485                 490                 495
Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
            500                 505                 510
Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
        515                 520                 525
Gln Gln Pro Phe Leu Glu Pro Thr His Thr Arg Ala Leu Ser Val Arg
    530                 535                 540
Gln Ala Pro Leu Ala Ala Val Gly Met Asp Gly Leu Glu Lys His Arg
545                 550                 555                 560
Leu Val Ser Arg Thr His Ser Ser Pro Ala Ala Ser Val Leu Pro His
                565                 570                 575
Pro Ala Met Asp Arg Pro Leu Gln Pro Gly Ser Ala Thr Gly Ile Ala
            580                 585                 590
Tyr Asp Pro Leu Met Leu Lys His Gln Cys Val Cys Gly Asn Ser Thr
        595                 600                 605
Thr His Pro Glu His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg Leu
    610                 615                 620
```

```
Gln Glu Thr Gly Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys
625                 630                 635                 640
Ala Ser Leu Glu Glu Ile Gln Leu Val His Ser Glu His His Ser Leu
                645                 650                 655
Leu Tyr Gly Thr Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile
            660                 665                 670
Leu Leu Gly Asp Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly
        675                 680                 685
Gly Leu Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser
    690                 695                 700
Gly Ala Ala Arg Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys
705                 710                 715                 720
Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
                725                 730                 735
Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
            740                 745                 750
Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
        755                 760                 765
Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
    770                 775                 780
Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
785                 790                 795                 800
Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
                805                 810                 815
Arg Phe Ile Ser Leu Glu Pro His Phe Tyr Leu Tyr Leu Ser Gly Asn
            820                 825                 830
Cys Ile Ala
        835
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<210> 9
<211> 1791
<212> DNA
<213> Homo sapiens

<400> 9

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ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca cttgcaggac 60
tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact ctaagccaga tggggtggct 120
ggacgagagc agctcttggc tcagcaaaga atgcacagta tgatcagctc agtggatgtg 180
aagtcagaag ttcctgtggg cctggagccc atctcacctt tagacctaag gacagacctc 240
aggatgatga tgcccgtggt ggaccctgtt gtccgtgaga agcaattgca gcaggaatta 300
cttcttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga gtttcagaaa 360
cagcatgaga acttgacacg gcagcaccag gctcagcttc aggagcatat caaggaactt 420
ctagccataa aacagcaaca agaactccta gaaaaggagc agaaactgga gcagcagagg 480
caagaacagg aagtagagag gcatcgcaga gaacagcagc ttcctcctct cagaggcaaa 540
gatagaggac gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc 600
ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca ttccgtgagc 660
cgccatccca agctctggta cacggctgcc caccacacat cattggatca aagctctcca 720
ccccttagtg gaacatctcc atcctacaag tacacattac caggagcaca agatgcaaag 780
gatgatttcc cccttcgaaa aactgaatcc tcagtcagta gcagttctcc aggctctggt 840
cccagttcac caaacaatgg gccaactgga agtgttactg aaaatgagac ttcggttttg 900
ccccctaccc ctcatgccga gcaaatggtt tcacagcaac gcattctaat tcatgaagat 960
tccatgaacc tgctaagtct ttatacctct ccttctttgc ccaacattac cttggggctt 1020
cccgcagtgc catcccagct caatgcttcg aattcactca aagaaaagca gaagtgtgag 1080
acgcagacgc ttaggcaagg tgttcctctg cctgggcagt atggaggcag catcccggca 1140
tcttccagcc accctcatgt tactttagag ggaaagccac ccaacagcag ccaccaggct 1200
ctcctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct tgtagctggt 1260
ggagttccct tacatcctca gtctcccttg gcaacaaaag agagaatttc acctggcatt 1320
agaggtaccc acaaattgcc ccgtcacaga cccctgaacc gaacccagtc tgcacctttg 1380
cctcagagca cgttggctca gctggtcatt caacagcaac accagcaatt cttggagaag 1440
cagaagcaat accagcagca gatccacatg aacaaactgc tttcgaaatc tattgaacaa 1500
ctgaagcaac caggcagtca ccttgaggaa gcagaggaag agcttcaggg ggaccaggcg 1560
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atgcaggaag acagagcgcc ctctagtggc aacagcacta ggagcgacag cagtgcttgt 1620
gtggatgaca cactgggaca agttggggct gtgaaggtca aggaggaacc agtggacagt 1680
gatgaagatg ctcagatcca ggaaatggaa tctggggagc aggctgcttt tatgcaacag 1740
gtaataggca aagatttagc tccaggattt gtaattaaag tcattatctg a 1791

<210> 10
<211> 546
<212> PRT
<213> Homo sapiens

<400> 10
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Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
20 25 30
Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
35 40 45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50 55 60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65 70 75 80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85 90 95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100 105 110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115 120 125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130 135 140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145 150 155 160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
165 170 175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
180 185 190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
195 200 205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
210 215 220
Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
225 230 235 240
Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
245 250 255
Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
260 265 270
Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
275 280 285
Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
290 295 300
Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
305 310 315 320
Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
325 330 335
Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
340 345 350
Gln His Leu Leu Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val
355 360 365
Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
370 375 380
Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
385 390 395 400
Pro Leu Asn Arg Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala

```
                405                 410                 415
Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
            420                 425                 430
Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
        435                 440                 445
Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
    450                 455                 460
Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
465                 470                 475                 480
Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
                485                 490                 495
Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
            500                 505                 510
Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
        515                 520                 525
Gln Gln Val Ile Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val
    530                 535                 540
Ile Ile
545
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<210> 11
<211> 590
<212> PRT
<213> Homo sapiens

<400> 11

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Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
 1               5                  10                  15
Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
            20                  25                  30
Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
        35                  40                  45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
    50                  55                  60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65                  70                  75                  80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
                85                  90                  95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
            100                 105                 110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
        115                 120                 125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
    130                 135                 140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145                 150                 155                 160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
                165                 170                 175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
            180                 185                 190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
        195                 200                 205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
    210                 215                 220
Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
225                 230                 235                 240
Pro Leu Leu Arg Arg Lys Asp Gly Asn Val Val Thr Ser Phe Lys Lys
                245                 250                 255
Arg Met Phe Glu Val Thr Glu Ser Ser Val Ser Ser Ser Ser Pro Gly
            260                 265                 270
Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly Ser Val Thr Glu
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275 280 285
Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala Glu Gln Met Val
290 295 300
Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met Asn Leu Leu Ser
305 310 315 320
Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu Gly Leu Pro Ala
325 330 335
Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys
340 345 350
Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr
355 360 365
Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His Val Thr Leu Glu
370 375 380
Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu
385 390 395 400
Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val Ala Gly Gly Val
405 410 415
Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu Arg Ile Ser Pro
420 425 430
Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg Pro Leu Asn Arg
435 440 445
Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala Gln Leu Val Ile
450 455 460
Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys Gln Tyr Gln Gln
465 470 475 480
Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile Glu Gln Leu Lys
485 490 495
Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu Leu Gln Gly Asp
500 505 510
Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly Asn Ser Thr Arg
515 520 525
Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly Gln Val Gly Ala
530 535 540
Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile
545 550 555 560
Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met Gln Gln Val Ile
565 570 575
Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val Ile Ile
580 585 590

<210> 12
<211> 1084
<212> PRT
<213> Homo sapiens

<400> 12
Met Ser Ser Gln Ser His Pro Asp Gly Leu Ser Gly Arg Asp Gln Pro
1 5 10 15
Val Glu Leu Leu Asn Pro Ala Arg Val Asn His Met Pro Ser Thr Val
20 25 30
Asp Val Ala Thr Ala Leu Pro Leu Gln Val Ala Pro Ser Ala Val Pro
35 40 45
Met Asp Leu Arg Leu Asp His Gln Phe Ser Leu Pro Val Ala Glu Pro
50 55 60
Ala Leu Arg Glu Gln Gln Leu Gln Gln Glu Leu Leu Ala Leu Lys Gln
65 70 75 80
Lys Gln Gln Ile Gln Arg Gln Ile Leu Ile Ala Glu Phe Gln Arg Gln
85 90 95
His Glu Gln Leu Ser Arg Gln His Glu Ala Gln Leu His Glu His Ile
100 105 110
Lys Gln Gln Gln Glu Met Leu Ala Met Lys His Gln Gln Glu Leu Leu

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        115                 120                 125
Glu His Gln Arg Lys Leu Glu Arg His Arg Gln Glu Gln Glu Leu Glu
    130                 135                 140
Lys Gln His Arg Glu Gln Lys Leu Gln Gln Leu Lys Asn Lys Glu Lys
145                 150                 155                 160
Gly Lys Glu Ser Ala Val Ala Ser Thr Glu Val Lys Met Lys Leu Gln
                165                 170                 175
Glu Phe Val Leu Asn Lys Lys Lys Ala Leu Ala His Arg Asn Leu Asn
            180                 185                 190
His Cys Ile Ser Ser Asp Pro Arg Tyr Trp Tyr Gly Lys Thr Gln His
        195                 200                 205
Ser Ser Leu Asp Gln Ser Ser Pro Pro Gln Ser Gly Val Ser Thr Ser
    210                 215                 220
Tyr Asn His Pro Val Leu Gly Met Tyr Asp Ala Lys Asp Asp Phe Pro
225                 230                 235                 240
Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu Lys Leu Arg Ser Arg Leu
                245                 250                 255
Lys Gln Lys Val Ala Glu Arg Arg Ser Ser Pro Leu Leu Arg Arg Lys
            260                 265                 270
Asp Gly Pro Val Val Thr Ala Leu Lys Lys Arg Pro Leu Asp Val Thr
        275                 280                 285
Asp Ser Ala Cys Ser Ser Ala Pro Gly Ser Gly Pro Ser Ser Pro Asn
    290                 295                 300
Asn Ser Ser Gly Ser Val Ser Ala Glu Asn Gly Ile Ala Pro Ala Val
305                 310                 315                 320
Pro Ser Ile Pro Ala Glu Thr Ser Leu Ala His Arg Leu Val Ala Arg
                325                 330                 335
Glu Gly Ser Ala Ala Pro Leu Pro Leu Tyr Thr Ser Pro Ser Leu Pro
            340                 345                 350
Asn Ile Thr Leu Gly Leu Pro Ala Thr Gly Pro Ser Ala Gly Thr Ala
        355                 360                 365
Gly Gln Gln Asp Thr Glu Arg Leu Thr Leu Pro Ala Leu Gln Gln Arg
    370                 375                 380
Leu Ser Leu Phe Pro Gly Thr His Leu Thr Pro Tyr Leu Ser Thr Ser
385                 390                 395                 400
Pro Leu Glu Arg Asp Gly Gly Ala Ala His Ser Pro Leu Leu Gln His
                405                 410                 415
Met Val Leu Leu Glu Gln Pro Pro Ala Gln Ala Pro Leu Val Thr Gly
            420                 425                 430
Leu Gly Ala Leu Pro Leu His Ala Gln Ser Leu Val Gly Ala Asp Arg
        435                 440                 445
Val Ser Pro Ser Ile His Lys Leu Arg Gln His Arg Pro Leu Gly Arg
    450                 455                 460
Thr Gln Ser Ala Pro Leu Pro Gln Asn Ala Gln Ala Leu Gln His Leu
465                 470                 475                 480
Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys His Lys Gln Gln
                485                 490                 495
Phe Gln Gln Gln Gln Leu Gln Met Asn Lys Ile Ile Pro Lys Pro Ser
            500                 505                 510
Glu Pro Ala Arg Gln Pro Glu Ser His Pro Glu Glu Thr Glu Glu Glu
        515                 520                 525
Leu Arg Glu His Gln Ala Leu Leu Asp Glu Pro Tyr Leu Asp Arg Leu
    530                 535                 540
Pro Gly Gln Lys Glu Ala His Ala Gln Ala Gly Val Gln Val Lys Gln
545                 550                 555                 560
Glu Pro Ile Glu Ser Asp Glu Glu Glu Ala Glu Pro Pro Arg Glu Val
                565                 570                 575
Glu Pro Gly Gln Arg Gln Pro Ser Glu Gln Glu Leu Leu Phe Arg Gln
            580                 585                 590
Gln Ala Leu Leu Leu Glu Gln Gln Arg Ile His Gln Leu Arg Asn Tyr
        595                 600                 605
Gln Ala Ser Met Glu Ala Ala Gly Ile Pro Val Ser Phe Gly Gly His
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    610                 615                 620
Arg Pro Leu Ser Arg Ala Gln Ser Ser Pro Ala Ser Ala Thr Phe Pro
625                 630                 635                 640
Val Ser Val Gln Glu Pro Pro Thr Lys Pro Arg Phe Thr Thr Gly Leu
                645                 650                 655
Val Tyr Asp Thr Leu Met Leu Lys His Gln Cys Thr Cys Gly Ser Ser
            660                 665                 670
Ser Ser His Pro Glu His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg
        675                 680                 685
Leu Gln Glu Thr Gly Leu Arg Gly Lys Cys Glu Cys Ile Arg Gly Arg
    690                 695                 700
Lys Ala Thr Leu Glu Glu Leu Gln Thr Val His Ser Glu Ala His Thr
705                 710                 715                 720
Leu Leu Tyr Gly Thr Asn Pro Leu Asn Arg Gln Lys Leu Asp Ser Lys
                725                 730                 735
Lys Leu Leu Gly Ser Leu Ala Ser Val Phe Val Arg Leu Pro Cys Gly
            740                 745                 750
Gly Val Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Val His Ser Ala
        755                 760                 765
Gly Ala Ala Arg Leu Ala Val Gly Cys Val Val Glu Leu Val Phe Lys
    770                 775                 780
Val Ala Thr Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
785                 790                 795                 800
Gly His His Ala Glu Glu Ser Thr Pro Met Gly Phe Cys Tyr Phe Asn
                805                 810                 815
Ser Val Ala Val Ala Ala Lys Leu Leu Gln Gln Arg Leu Ser Val Ser
            820                 825                 830
Lys Ile Leu Ile Val Asp Trp Asp Val His His Gly Asn Gly Thr Gln
        835                 840                 845
Gln Ala Phe Tyr Ser Asp Pro Ser Val Leu Tyr Met Ser Leu His Arg
    850                 855                 860
Tyr Asp Asp Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asp Glu Val
865                 870                 875                 880
Gly Thr Gly Pro Gly Val Gly Phe Asn Val Asn Met Ala Phe Thr Gly
                885                 890                 895
Gly Leu Asp Pro Pro Met Gly Asp Ala Glu Tyr Leu Ala Ala Phe Arg
            900                 905                 910
Thr Val Val Met Pro Ile Ala Ser Glu Phe Ala Pro Asp Val Val Leu
        915                 920                 925
Val Ser Ser Gly Phe Asp Ala Val Glu Gly His Pro Thr Pro Leu Gly
    930                 935                 940
Gly Tyr Asn Leu Ser Ala Arg Cys Phe Gly Tyr Leu Thr Lys Gln Leu
945                 950                 955                 960
Met Gly Leu Ala Gly Gly Arg Ile Val Leu Ala Leu Glu Gly Gly His
                965                 970                 975
Asp Leu Thr Ala Ile Cys Asp Ala Ser Glu Ala Cys Val Ser Ala Leu
            980                 985                 990
Leu Gly Asn Glu Leu Asp Pro Leu Pro Glu Lys Val Leu Gln Gln Arg
        995                 1000                1005
Pro Asn Ala Asn Ala Val Arg Ser Met Glu Lys Val Met Glu Ile His
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Glu Ile Gln Leu Val His Ser Glu His His Ser Leu Leu Tyr Gly Thr
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Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile Leu Leu Gly Asp
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Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser Gly Ala Ala Arg
            740                 745                 750
Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys Val Ala Ser Gly
        755                 760                 765
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Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn Ser Val Ala Ile
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        35                  40                  45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
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Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65                  70                  75                  80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
                85                  90                  95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
            100                 105                 110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
        115                 120                 125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
    130                 135                 140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145                 150                 155                 160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
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Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
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Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
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225 230 235 240
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245 250 255
Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
260 265 270
Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
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Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
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Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
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Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
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705                 710                 715                 720
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Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
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Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
785                 790                 795                 800
Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
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Thr Ile Val Lys Pro Val Ala Lys Glu Phe Asp Pro Asp Met Val Leu
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865                 870                 875                 880
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Met Thr Leu Ala Asp Gly Arg Val Val Leu Ala Leu Glu Gly Gly His
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Leu Gly Asn Glu Leu Glu Pro Leu Ala Glu Asp Ile Leu His Gln Ser
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ctagccataa aacagcaaca agaactccta gaaaaggagc agaaactgga gcagcagagg 480
caagaacagg aagtagagag gcatcgcaga gaacagcagc ttcctcctct cagaggcaaa 540
gatagaggac gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc 600
ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca ttccgtgagc 660
cgccatccca agctctggta cacggctgcc caccacacat cattggatca aagctctcca 720
ccccttagtg gaacatctcc atcctacaag tacacattac caggagcaca agatgcaaag 780
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tccatgaacc tgctaagtct ttatacctct ccttctttgc ccaacattac cttggggctt 1020
cccgcagtgc catcccagct caatgcttcg aattcactca aagaaaagca gaagtgtgag 1080
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cagaagcaat accagcagca gatccacatg aacaaactgc tttcgaaatc tattgaacaa 1500
ctgaagcaac caggcagtca ccttgaggaa gcagaggaag agcttcaggg ggaccaggcg 1560
atgcaggaag acagagcgcc ctctagtggc aacagcacta ggagcgacag cagtgcttgt 1620
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gttggcatgg atggattaga gaaacaccgt ctcgtctcca ggactcactc ttcccctgct 1860
gcctctgttt tacctcaccc agcaatggac cgcccccctcc agcctggctc tgcaactgga 1920
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cctgagcatg ctggacgaat acagagtatc tggtcacgac tgcaagaaac tgggctgcta 2040
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ggggtggaca gtgacaccat ttggaatgag ctacactcgt ccggtgctgc acgcatggct 2280
gttggctgtg tcatcgagct ggcttccaaa gtggcctcag gagagctgaa gaatgggttt 2340
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ggctctagaa ggaggacatg atctcacagc catctgtgat gcatcagaag cctgtgtaaa 3240
tgcccttcta ggaaatgagc tggagccact tgcagaagat attctccacc aaagcccgaa 3300
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ctcttaa 3367

<210> 8
<211> 835
<212> PRT
<213> Homo sapiens

<400> 8
Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
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Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
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Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
35 40 45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50 55 60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65 70 75 80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85 90 95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100 105 110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115 120 125

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Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
    130                 135                 140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145                 150                 155                 160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
                165                 170                 175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
            180                 185                 190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
        195                 200                 205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
    210                 215                 220
Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
225                 230                 235                 240
Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
                245                 250                 255
Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
            260                 265                 270
Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
        275                 280                 285
Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
    290                 295                 300
Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
305                 310                 315                 320
Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
                325                 330                 335
Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
            340                 345                 350
Gln His Leu Leu Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val
        355                 360                 365
Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
    370                 375                 380
Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
385                 390                 395                 400
Pro Leu Asn Arg Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala
                405                 410                 415
Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
            420                 425                 430
Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
        435                 440                 445
Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
    450                 455                 460
Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
465                 470                 475                 480
Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
                485                 490                 495
Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
            500                 505                 510
Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
        515                 520                 525
Gln Gln Pro Phe Leu Glu Pro Thr His Thr Arg Ala Leu Ser Val Arg
    530                 535                 540
Gln Ala Pro Leu Ala Ala Val Gly Met Asp Gly Leu Glu Lys His Arg
545                 550                 555                 560
Leu Val Ser Arg Thr His Ser Ser Pro Ala Ala Ser Val Leu Pro His
                565                 570                 575
Pro Ala Met Asp Arg Pro Leu Gln Pro Gly Ser Ala Thr Gly Ile Ala
            580                 585                 590
Tyr Asp Pro Leu Met Leu Lys His Gln Cys Val Cys Gly Asn Ser Thr
        595                 600                 605
Thr His Pro Glu His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg Leu
    610                 615                 620
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Gln Glu Thr Gly Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys
625                 630                 635                 640
Ala Ser Leu Glu Glu Ile Gln Leu Val His Ser Glu His His Ser Leu
                645                 650                 655
Leu Tyr Gly Thr Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile
            660                 665                 670
Leu Leu Gly Asp Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly
        675                 680                 685
Gly Leu Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser
    690                 695                 700
Gly Ala Ala Arg Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys
705                 710                 715                 720
Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
                725                 730                 735
Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
            740                 745                 750
Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
        755                 760                 765
Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
    770                 775                 780
Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
785                 790                 795                 800
Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
                805                 810                 815
Arg Phe Ile Ser Leu Glu Pro His Phe Tyr Leu Tyr Leu Ser Gly Asn
            820                 825                 830
Cys Ile Ala
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<210> 9
<211> 1791
<212> DNA
<213> Homo sapiens

<400> 9

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tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact ctaagccaga tggggtggct 120
ggacgagagc agctcttggc tcagcaaaga atgcacagta tgatcagctc agtggatgtg 180
aagtcagaag ttcctgtggg cctggagccc atctcacctt tagacctaag gacagacctc 240
aggatgatga tgcccgtggt ggaccctgtt gtccgtgaga agcaattgca gcaggaatta 300
cttcttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga gtttcagaaa 360
cagcatgaga acttgacacg gcagcaccag gctcagcttc aggagcatat caaggaactt 420
ctagccataa aacagcaaca agaactccta gaaaaggagc agaaactgga gcagcagagg 480
caagaacagg aagtagagag gcatcgcaga gaacagcagc ttcctcctct cagaggcaaa 540
gatagaggac gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc 600
ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca ttccgtgagc 660
cgccatccca agctctggta cacggctgcc caccacacat cattggatca aagctctcca 720
ccccttagtg gaacatctcc atcctacaag tacacattac caggagcaca agatgcaaag 780
gatgatttcc cccttcgaaa aactgaatcc tcagtcagta gcagttctcc aggctctggt 840
cccagttcac caaacaatgg gccaactgga agtgttactg aaaatgagac ttcggttttg 900
ccccctaccc ctcatgccga gcaaatggtt tcacagcaac gcattctaat tcatgaagat 960
tccatgaacc tgctaagtct ttatacctct ccttctttgc ccaacattac cttggggctt 1020
cccgcagtgc catcccagct caatgcttcg aattcactca aagaaaagca gaagtgtgag 1080
acgcagacgc ttaggcaagg tgttcctctg cctgggcagt atggaggcag catcccggca 1140
tcttccagcc accctcatgt tactttagag ggaaagccac ccaacagcag ccaccaggct 1200
ctcctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct tgtagctggt 1260
ggagttccct tacatcctca gtctcccttg gcaacaaaag agagaatttc acctggcatt 1320
agaggtaccc acaaattgcc ccgtcacaga cccctgaacc gaacccagtc tgcacctttg 1380
cctcagagca cgttggctca gctggtcatt caacagcaac accagcaatt cttggagaag 1440
cagaagcaat accagcagca gatccacatg aacaaactgc tttcgaaatc tattgaacaa 1500
ctgaagcaac caggcagtca ccttgaggaa gcagaggaag agcttcaggg ggaccaggcg 1560
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atgcaggaag acagagcgcc ctctagtggc aacagcacta ggagcgacag cagtgcttgt 1620
gtggatgaca cactgggaca agttggggct gtgaaggtca aggaggaacc agtggacagt 1680
gatgaagatg ctcagatcca ggaaatggaa tctggggagc aggctgcttt tatgcaacag 1740
gtaataggca aagatttagc tccaggattt gtaattaaag tcattatctg a 1791

<210> 10
<211> 546
<212> PRT
<213> Homo sapiens

<400> 10
Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
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Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
20 25 30
Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
35 40 45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50 55 60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65 70 75 80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85 90 95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100 105 110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115 120 125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130 135 140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145 150 155 160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
165 170 175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
180 185 190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
195 200 205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
210 215 220
Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
225 230 235 240
Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
245 250 255
Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
260 265 270
Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
275 280 285
Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
290 295 300
Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
305 310 315 320
Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
325 330 335
Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
340 345 350
Gln His Leu Leu Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val
355 360 365
Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
370 375 380
Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
385 390 395 400
Pro Leu Asn Arg Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala

Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
405 410 415
Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
420 425 430
Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
435 440 445
Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
450 455 460
465 470 475 480
Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
485 490 495
Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
500 505 510
Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
515 520 525
Gln Gln Val Ile Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val
530 535 540
Ile Ile
545

<210> 11
<211> 590
<212> PRT
<213> Homo sapiens

<400> 11
Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
1 5 10 15
Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
20 25 30
Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
35 40 45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50 55 60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65 70 75 80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85 90 95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100 105 110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115 120 125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130 135 140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145 150 155 160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
165 170 175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
180 185 190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
195 200 205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
210 215 220
Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
225 230 235 240
Pro Leu Leu Arg Arg Lys Asp Gly Asn Val Val Thr Ser Phe Lys Lys
245 250 255
Arg Met Phe Glu Val Thr Glu Ser Ser Val Ser Ser Ser Ser Pro Gly
260 265 270
Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly Ser Val Thr Glu

275 280 285
Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala Glu Gln Met Val
290 295 300
Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met Asn Leu Leu Ser
305 310 315 320
Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu Gly Leu Pro Ala
325 330 335
Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys
340 345 350
Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr
355 360 365
Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His Val Thr Leu Glu
370 375 380
Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu
385 390 395 400
Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val Ala Gly Gly Val
405 410 415
Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu Arg Ile Ser Pro
420 425 430
Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg Pro Leu Asn Arg
435 440 445
Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala Gln Leu Val Ile
450 455 460
Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys Gln Tyr Gln Gln
465 470 475 480
Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile Glu Gln Leu Lys
485 490 495
Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu Leu Gln Gly Asp
500 505 510
Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly Asn Ser Thr Arg
515 520 525
Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly Gln Val Gly Ala
530 535 540
Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile
545 550 555 560
Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met Gln Gln Val Ile
565 570 575
Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val Ile Ile
580 585 590

<210> 12
<211> 1084
<212> PRT
<213> Homo sapiens

<400> 12
Met Ser Ser Gln Ser His Pro Asp Gly Leu Ser Gly Arg Asp Gln Pro
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Val Glu Leu Leu Asn Pro Ala Arg Val Asn His Met Pro Ser Thr Val
20 25 30
Asp Val Ala Thr Ala Leu Pro Leu Gln Val Ala Pro Ser Ala Val Pro
35 40 45
Met Asp Leu Arg Leu Asp His Gln Phe Ser Leu Pro Val Ala Glu Pro
50 55 60
Ala Leu Arg Glu Gln Gln Leu Gln Gln Glu Leu Leu Ala Leu Lys Gln
65 70 75 80
Lys Gln Gln Ile Gln Arg Gln Ile Leu Ile Ala Glu Phe Gln Arg Gln
85 90 95
His Glu Gln Leu Ser Arg Gln His Glu Ala Gln Leu His Glu His Ile
100 105 110
Lys Gln Gln Gln Glu Met Leu Ala Met Lys His Gln Gln Glu Leu Leu

115 120 125
Glu His Gln Arg Lys Leu Glu Arg His Arg Gln Glu Gln Glu Leu Glu
130 135 140
Lys Gln His Arg Glu Gln Lys Leu Gln Gln Leu Lys Asn Lys Glu Lys
145 150 155 160
Gly Lys Glu Ser Ala Val Ala Ser Thr Glu Val Lys Met Lys Leu Gln
165 170 175
Glu Phe Val Leu Asn Lys Lys Lys Ala Leu Ala His Arg Asn Leu Asn
180 185 190
His Cys Ile Ser Ser Asp Pro Arg Tyr Trp Tyr Gly Lys Thr Gln His
195 200 205
Ser Ser Leu Asp Gln Ser Ser Pro Pro Gln Ser Gly Val Ser Thr Ser
210 215 220
Tyr Asn His Pro Val Leu Gly Met Tyr Asp Ala Lys Asp Asp Phe Pro
225 230 235 240
Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu Lys Leu Arg Ser Arg Leu
245 250 255
Lys Gln Lys Val Ala Glu Arg Arg Ser Ser Pro Leu Leu Arg Arg Lys
260 265 270
Asp Gly Pro Val Val Thr Ala Leu Lys Lys Arg Pro Leu Asp Val Thr
275 280 285
Asp Ser Ala Cys Ser Ser Ala Pro Gly Ser Gly Pro Ser Ser Pro Asn
290 295 300
Asn Ser Ser Gly Ser Val Ser Ala Glu Asn Gly Ile Ala Pro Ala Val
305 310 315 320
Pro Ser Ile Pro Ala Glu Thr Ser Leu Ala His Arg Leu Val Ala Arg
325 330 335
Glu Gly Ser Ala Ala Pro Leu Pro Leu Tyr Thr Ser Pro Ser Leu Pro
340 345 350
Asn Ile Thr Leu Gly Leu Pro Ala Thr Gly Pro Ser Ala Gly Thr Ala
355 360 365
Gly Gln Gln Asp Thr Glu Arg Leu Thr Leu Pro Ala Leu Gln Gln Arg
370 375 380
Leu Ser Leu Phe Pro Gly Thr His Leu Thr Pro Tyr Leu Ser Thr Ser
385 390 395 400
Pro Leu Glu Arg Asp Gly Gly Ala Ala His Ser Pro Leu Leu Gln His
405 410 415
Met Val Leu Leu Glu Gln Pro Pro Ala Gln Ala Pro Leu Val Thr Gly
420 425 430
Leu Gly Ala Leu Pro Leu His Ala Gln Ser Leu Val Gly Ala Asp Arg
435 440 445
Val Ser Pro Ser Ile His Lys Leu Arg Gln His Arg Pro Leu Gly Arg
450 455 460
Thr Gln Ser Ala Pro Leu Pro Gln Asn Ala Gln Ala Leu Gln His Leu
465 470 475 480
Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys His Lys Gln Gln
485 490 495
Phe Gln Gln Gln Gln Leu Gln Met Asn Lys Ile Ile Pro Lys Pro Ser
500 505 510
Glu Pro Ala Arg Gln Pro Glu Ser His Pro Glu Glu Thr Glu Glu Glu
515 520 525
Leu Arg Glu His Gln Ala Leu Leu Asp Glu Pro Tyr Leu Asp Arg Leu
530 535 540
Pro Gly Gln Lys Glu Ala His Ala Gln Ala Gly Val Gln Val Lys Gln
545 550 555 560
Glu Pro Ile Glu Ser Asp Glu Glu Glu Ala Glu Pro Pro Arg Glu Val
565 570 575
Glu Pro Gly Gln Arg Gln Pro Ser Glu Gln Glu Leu Leu Phe Arg Gln
580 585 590
Gln Ala Leu Leu Leu Glu Gln Gln Arg Ile His Gln Leu Arg Asn Tyr
595 600 605
Gln Ala Ser Met Glu Ala Ala Gly Ile Pro Val Ser Phe Gly Gly His

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    610                 615                 620
Arg Pro Leu Ser Arg Ala Gln Ser Ser Pro Ala Ser Ala Thr Phe Pro
625                 630                 635                 640
Val Ser Val Gln Glu Pro Pro Thr Lys Pro Arg Phe Thr Thr Gly Leu
                645                 650                 655
Val Tyr Asp Thr Leu Met Leu Lys His Gln Cys Thr Cys Gly Ser Ser
            660                 665                 670
Ser Ser His Pro Glu His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg
        675                 680                 685
Leu Gln Glu Thr Gly Leu Arg Gly Lys Cys Glu Cys Ile Arg Gly Arg
    690                 695                 700
Lys Ala Thr Leu Glu Glu Leu Gln Thr Val His Ser Glu Ala His Thr
705                 710                 715                 720
Leu Leu Tyr Gly Thr Asn Pro Leu Asn Arg Gln Lys Leu Asp Ser Lys
                725                 730                 735
Lys Leu Leu Gly Ser Leu Ala Ser Val Phe Val Arg Leu Pro Cys Gly
            740                 745                 750
Gly Val Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Val His Ser Ala
        755                 760                 765
Gly Ala Ala Arg Leu Ala Val Gly Cys Val Val Glu Leu Val Phe Lys
    770                 775                 780
Val Ala Thr Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
785                 790                 795                 800
Gly His His Ala Glu Glu Ser Thr Pro Met Gly Phe Cys Tyr Phe Asn
                805                 810                 815
Ser Val Ala Val Ala Ala Lys Leu Leu Gln Gln Arg Leu Ser Val Ser
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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report: 13 November 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/102984 A3

(54) Title: HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

(57) Abstract: The present invention features substantially pure HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), an HDRP(ΔNLS) polypeptides, and isolated nucleic acid molecules encoding those polypeptides. The present invention also features vectors containing*HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS),* and *HDRP(ΔNLS)* nucleic acid sequences, and cells containing those vectors.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/19051

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 9/78, 9/00, 9/14, 1/20, 15/00; C07H 21/04
US CL : 435/227, 183, 195, 252.3, 320.1; 536/23.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/227, 183, 195, 252.3, 320.1; 536/23.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN AND WEST. Sequence search in Swissprot, EST, N-GeneSeq, PIR_71, SPTREMBL & issued US patents.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAGASE et al. Prediction of Coding Sequences of Unidentified Human Genes. XI. The Complete Sequences of 100 New cDNA Clones from Brain Which Code for Large Proteins in Vitro. DNA Research November 1998, Vol 5, pages 277-286. See Table 1, Accession No. AB018287 is 58.8% similar to DNA sequence of SEQ IF SEQ ID NO : 1, claim 4 (g).	4
A, P	ZHOU et al. Cloning and Characterization of a histone deacetylase, HDAC9. PNAS, 11 September 2001, Vol. 98, No. 19, pages 10572-10577.	1-9, 29
A	WANG et al. HDAC4, a Human Histone Deacetylase Related to Yeast HDA1, Is a Transcriptional Corepressor. Molecular and Cellular Biology, November 1999, Vol. 19, No. 11, pages 7816-7827.	1-9, 29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 30 October 2002 (30.10.2002)	Date of mailing of the international search report 13 MAR 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Tekchand Saidha Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/19051

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-9 & 29 (SEQ ID NOS : 1 & 2)

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/19051

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-9, 29, drawn to isolated nucleic acid, the encoded protein and protein composition.

Group II, claim(s) 10, drawn to antibody.

Group III, claim(s) 11-13, drawn to a method of identifying a compound - modulate DNA expression.

Group IV, claim(s) 14-19, 33, drawn to a method of identifying a compound that modulate enzymatic activity.

Group V, claim(s) 20-25, 34, drawn to a method of identifying a compound that modulate transcriptional repression activity of the polypeptide.

Group VI, claim(s) 26-27, drawn to a method of identifying a compound that modulate expression of a nucleic acid molecule.

Group VII, claim(s) 28, drawn to a method of identifying a polypeptide that interacts with a polypeptide of claim 1 in a two-hybrid system.

Group VIII, claim(s) 30-32, drawn to a method of diagnosing a cell proliferation disease.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

1. SEQ ID NO : 1 and 2 [HDAC9].
2. SEQ ID NO : 3 and 4 [HDAC9a].
3. SEQ ID NO : 5 and 6 [HDAC9-ΔNLS].
4. SEQ ID NO : 7 and 8 [HDAC9a-ΔNLS].
5. SEQ ID NO : 9 and 10 [HDRP-ΔNLS].

The claims are deemed to correspond to the species listed above in the following manner:

Each of the claims listed in groups I-VIII correspond to each of the 5 species which are structurally distinct.

The following claim(s) are generic: 1-5.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I has a special technical feature of the nucleotide sequence encoding a specific histone deacetylase which Groups II-VIII do not share; Group II has a special technical feature of the antibody to a specific histone deacetylase which Groups I & III-VIII do not share; Groups III-VIII employ nucleic acid or polypeptide in various method of identifying compounds or polypeptides for distinct uses. Further, in view of 37 CFR 1.475 (b), when claims corresponding to different categories of inventions are present then only (3) applies and additional methods of use are deemed to lack unity.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The various species correspond to nucleic acid and polypeptide sequences which are structurally and in activity distinct from each other, therefore lack the same or corresponding special technical feature.